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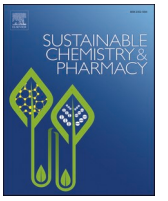

# Eco-pharma dilemma: Navigating environmental sustainability trade-offs within the lifecycle of pharmaceuticals – A comment

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ABSTRACT

An ideal pharmaceutical treatment is both safe and effective for patients. However, from a sustainability perspective, it also needs to be cost-effective, energy- and resource-efficient, and not have a negative impact on the environment. When striving towards environmentally sustainable healthcare, trade-offs between environmental sustainability and other aspects play a multifaceted role in decision-making along the whole life cycle of a pharmaceutical, from design to end-of-life. When making environment-driven choices, stakeholders in this life cycle (e.g., procurers, prescribers) may not be aware of all consequences (environmental, social, or economic), which complicates decision-making processes. Information at hand may be ambiguous or unknown due to data gaps, complex and interdependent local, national and global healthcare systems, and unknown future developments. Thus, trade-offs may happen at temporal or spatial scales outside of the daily practice of stakeholders. This commentary aims to initiate a discussion on these trade-offs, the need for a holistic view, the use of multi-criteria decision-making tools, and clear environmental sustainability guidelines.

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**Abbreviations (for footnote on first page)**

AI – Artificial Intelligence
API – Active Pharmaceutical Ingredient
HTA – Health Technology Assessment
LCSA – Life Cycle Sustainability Assessment
PFAS – Per- and polyFluoroAlkyl Substancs
REACH – Registration, Evaluation and Authorization of Chemicals
SSbD – Safe and Sustainable by Design

## 1. Introduction

Pharmaceutical treatment plays and essential role in improving human health, but production of pharmaceutical products, their distribution, use and disposal negatively impacts planetary health. The healthcare sector is an important environmental polluter (Healthcare Without Harm. Healthcare's climate footprint, 2019; Richie, 2022) responsible for about 4.4% of the global carbon footprint, within which, the pharmaceutical sector is a major contributor (Healthcare Without Harm. Healthcare's climate footprint, 2019; Belkhir and Elmeligi, 2019; Pichler et al., 2019; Lenzen et al., 2020; Steenmeijer et al., 2022a,b). In addition to the carbon footprint, many active pharmaceutical ingredients (APIs) are detected in watercourses (Wilkinson et al., 2022) because of emissions after use (post consumption excretion by patients), improper disposal of unused medicines, and manufacturing in countries with little or no environmental regulation (OECD, 2019). Their presence in water systems limits the availability of safe and clean drinking water, affects biodiversity (Damiana et al., 2019; Tyler and Goodhead, 2010; Domingo-Echabaru et al., 2021), and thus impacts human health and overall environmental sustainability. With the One Health (World Health Organization 2024) and Planetary Health (Planetary Health Alliance, 2024) approaches gaining momentum, it becomes essential to care for human health without compromising healthy environmental ecosystems.

Regretfully, environmental impacts of pharmaceuticals do not always run in parallel. For instance, pharmaceutical treatments that impact the aquatic environment less, may have a higher carbon footprint as a consequence, and vice versa. This commentary paper focusses on such trade-offs, as defined by the IPBES (Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services) as "*a situation where an improvement in the status of one aspect of the environment or of human well-being is necessarily associated with a decline in or loss of a different aspect. Trade-offs characterize most complex systems and are important to consider when making decisions that aim to improve environmental and/or socio-economic outcomes.*" (IPBES, 2024). Besides trade-offs, the IPBES also mentions synergies (also referred to as win-scenarios: "*synergies arise when the enhancement of one desirable outcome leads to enhancement of another*.

Many stakeholders within the life cycle of pharmaceutical products are already taking measures to reduce the environmental impact of pharmaceuticals (Moermond and de Rooy, 2022; Thornber et al., 2022; Sustainable Markets Initiative, 2023). For example, positive interventions are being made during the design and manufacture of APIs through the adoption of green chemistry principles (Ang et al., 2021; Leder et al., 2021; Moermond et al., 2022; ACS, 2024). Measures to reduce environmental impact post point of sale (in the consumer use phase) such as reimbursement, prescription and procurement are being trialled, with the aim to use products that impact the environment less (Richie, 2022; Moermond and de Rooy, 2022; Ruiz, 2023; NHS, 2024; Norwegian Hospital Procurement Trust, 2024). These choices between medicinal products are often driven by guidelines or policies, which are based on known trade-offs that are well embedded in most healthcare systems, including efficacy and safety (side effects), availability of treatment (e.g., waiting times for psychiatrists) and cost-effectiveness of treatment. Environmental sustainability is considered only on an *ad hoc* basis depending on personal interest of the stakeholder (e.g., industry, healthcare provider or patient). Furthermore, which aspects of environmental sustainability are perceived as most important (e.g., carbon footprint, land use, impact on biodiversity in surface waters) may depend on who makes the decision and for whom (patient, company, society, healthcare system, planet) (Heni et al., 2023). To date, there is no operational systematic approach to facilitate holistic decision-making that encompasses environmental sustainability and which takes into account the possible trade-offs between environmental sustainability aspects and other (patient health, economic and social) aspects along different stages of the life cycle.

This commentary aims to initiate a discussion on trade-offs that apply to environmental sustainability related to the entire life cycle of a pharmaceutical, from development to manufacture to use and end-of-life, and how healthcare professionals and policy makers should deal with this. These trade-offs may be known and unknown, or (un)consciously not taken into account if a holistic approach is lacking. In this commentary, we therefore provide examples to illustrate different types of trade-offs, with the aim of creating awareness and avoiding negative consequences of known and unknown trade-offs in the future. We also discuss synergies that could emerge when known trade-offs are dealt with, optimizing environmental sustainability. To this end, we use system thinking to identify


**Fig. 1.** Life cycle of a pharmaceutical, from discovery to end-of-life. Figure based on van Wilder et al. (2024).

trade-offs between various environmental impact categories, in various stages of the life cycle (Fig. 1). This life cycle, further described in Van Wilder et al. (2024), includes all stages starting at early discovery of active pharmaceutical ingredients and development of products, continuing to prescription and use by patients, and finally the end-of life (waste) stage.

With this commentary we aim to raise awareness about the complexity of trade-offs to a wider audience, such as healthcare professionals who wish to make decisions for environmental sustainability, but are often unaware of the consequences.

## 2. Environmental sustainability trade-offs for pharmaceuticals: choices and consequences

### 2.1. Examples

Table 1 exemplifies a range of trade-offs that occur along the life cycle of a pharmaceutical, as depicted in Fig. 1. As a group of experts on this topic, we have chosen examples for different aspects along the life-cycle, based on information from our professional networks, our own personal knowledge and experience, knowing that also this is limited and, just like other stakeholders, we may also not see all possible trade-offs. Because of these hiden aspects, a systematic review to identify these types of trade-offs is likely to be unfeasible. As the aim of our commentary is awareness raising, the identified topics in the table should indeed be seen as illustrative examples. Obvious trade-offs like costs and efficacy/safety for patients are not further elaborated in the table.

### 2.2. Spatial and temporal complexity

Already at the R&D phase, the intended use of a pharmaceutical and its molecular characteristics determine the potential impact after use via exposure and effects in the water system (Moermond et al., 2022). Parameters with a role in pharmaceutical research and development (such as stability, potency and specificity) and those that determine environmental fate and impact (such as environmental persistence, mobility, bioaccumulation and ecotoxicity) are (mutually) inter-related and may counteract; e.g., ecotoxicity at low concentrations is undesired (Moermond et al., 2022) but may go hand in hand with specifically acting low-dose active ingredients (Vidaurre et al., 2024).

Typically, patient and economic considerations prevail when decisions need to be made between different pharmaceutical treatments. However, environmental considerations could also be taken into account, when making sustainable choices for e.g., procurement or prescription guidelines. Within this context, trade-offs are not yet always obvious, due to spatial and temporal complexity in healthcare systems. This may lead to unintended and/or undesired consequences, e.g., a ban on all PFAS substances or another undesired chemical in the environment, may severely affect availability of globally important medicines (Table 1; examples 2 and 3), including treatment for COVID-19. On the other hand, this could also lead to innovation, e.g., creation of hydrophobic surfaces by physical treatment instead of PFAS-type molecules. Moving production from the Far East back to the EU or USA (Table 1, examples 3 and 5), as desired by the European Commission to secure supply, would also lead to production sites needing to adhere to European discharge limits, which will become virtually impossible if PFAS substances or equipment needed for their production are banned. Besides this, trade-offs may then also arise on a global scale with agreements on free trade (Table 1, example 5).

When environment-driven pharmaceutical treatment options lead to more hospitalizations or human safety issues (Table 1, examples 8 and 10), the overall outcome could potentially be less sustainable than the original treatment. Conversely, a more environmentally sustainable treatment can also lead to less hospitalization and less side effects (e.g., specific antibodies against cancer with fewer side effects vs chemotherapy with more side effects), which would be a synergy or win/win situation. Hence, ideally the complete healthcare pathway is considered when deciding on the most sustainable option. The final choice, although sometimes also the preferred choice from a medical perspective, may also depend on other factors. For example, as shown in Table 1, example 6, when psychotherapy instead of antidepressant use is not possible because of waiting lists or reimbursement rules.

Sometimes trade-offs are not at the same spatial scale and may be dynamic in nature. For example, the production of some APIs in the Far East and Asia, which pollutes the local environment, whilst the therapeutic benefit and user resides in other continents. Local effects may differ depending on where the patient is situated, e.g., effects on water systems after use may be much more severe in areas where sanitation is limited (Table 1, example 12) or where (treated) wastewater is needed for irrigation. Some of the consequences may also be different over time. In many of the examples in Table 1 (examples 1, 4, 6, 8, 9, 11, 12) energy use is a major trade-off, which in future may be less relevant with an ever-increasing uptake of renewable energy. Besides this, an increased cost of treatment (e.g, due to higher production costs (examples 1 and 4) or cost of psychotherapy (example 6) may also lead to social inequities.

### 2.3. Synergies

Besides trade-offs, synergies between different aspects of environmental sustainability and pharmaceutical treatment also need to be considered. For example, non-API treatments combined with lifestyle changes, reducing polypharmacy (Vermehren and Westergaard, 2022), re-dispensing expensive drugs (Table 1, example 10) or reducing unnecessary use of (over the counter) medication, lead to patient benefits, lower environmental footprint due to less pharmaceutical production, and less pharmaceutical residues in the environment. Some pharmaceutical treatment options may be beneficial to the environment and to the patient in the long-term. E.g., use of nano-carriers may lead to less use of APIs and less associated side effects (Table 1, example 1) and use of intravenous anaesthetics does not only reduce greenhouse gas emissions but also has advantages in postoperative recover (Kampman et al., 2024). Transparently identifying trade-offs can open doors to synergistic opportunities, such as implementing measures to transform these trade-offs into mutually beneficial outcomes. A focus on environmental sustainability can steer innovation and thus provide business

**Table 1**
Examples of mitigation options to reduce environmental impact, with their trade-offs regarding environmental and/or socio-economic aspects, grouped by life cycle stage.

| Mitigation options to reduce environmental impact | Trade-offs | |
|---|---|---|
| | Environmental aspects | Social and economic aspects[a] |
| ***Development of pharmaceutical productss production and distribution*** | | |
| 1. Nano-carriers are developed to improve the localization and release of APIs to the intended biological target, thereby reducing the dosing and associated side effects for the patient (Krishnan et al., 2023), and reducing the amount of API released into the environment (Jung et al., 2021). | The amount of energy, starting materials and use of auxiliaries needed to produce inorganic or organic nano-carriers may exceed that of the API production, but much is still unknown (OECD, Advanced Materials: Case Study on NanoCarriers - Workshop Report \| OECD. Besides this, the release of certain inorganic nanoparticles, such as gold, into the environment is undesired because of their persistence (Bundshuh et al., 2018). | As metals cannot be synthesized (being chemical elements) such applications result in depletion of the respective metal in the environment. They are not accessible for further use or other applications anymore. |
| 2. There is an increasing regulatory push to ban the use of the Per- and polyFluoroAlkyl Substances (PFAS) in the EU because of their extreme persistence and additional concerns for human health and the environment.<br>Some pharmaceuticals are PFAS compounds (i.e., contain a CF3 group), which often enhances metabolic stability in the patient's body and thus efficacy of treatment. However, after use the per- or poly-fluorinated fragment(s) will not further degrade in the environment and thus the ultimate degradation products (also being a PFAS) will remain there (Straub et al., 2023). | | The EU has published a legislative proposal, which is currently under further discussion and construction. In this proposal, a derogation for PFAS APIs has been proposed (ECHA, 2023). If PFAS APIs would not be exempt in the final ban, then patients would no longer have access to these medications (after a certain transition period). This will also affect pharmaceutical innovation; it would not be possible to further develop unique treatments such as the COVID-19 treatment Nirmatrelvir, an API with a perfluoro-group (PFAS) in the drug molecule (Drugbank, 2024). These aspects are all part of the socio-economic considerations in the REACH restriction process. |
| 3. The proposed legislative ban (see example 2) would also apply to PFAS substances that are used in pharmaceutical R&D, API production and pharmaceutical analysis. PFAS substances are used to produce APIs with and without a PFAS moiety. | An EU ban on PFAS substances may keep production of APIs out of the EU, where legislation to prevent emissions may be not so strict. This will also result in higher transportation impacts and relocation of environmental impacts to other parts of the world. | The proposed ban of PFAS substances in the EU will impact the way in which APIs are produced. New production equipment and methods will need to be developed and regulatory approval will need to be obtained. If technically feasible, this will be a costly operation affecting many APIs, part of which are produced as generics with extremely low margins. Not only because production processes need to be adapted, but also because all registration dossiers need to be updated, sometimes with new testing. As imports of classical produced APIs into the EU will be allowed, a PFAS restriction may keep production of APIs outside of the EU, which contrasts to the desire of the European Commission to move production back to the EU to secure supply (European Commission, 2020), and thus lead to a greater dependency on other countries. |
| 4. The use of biologicals to replace small molecule APIs, or reduce their dosing, reduces the end-of-life impacts of APIs. Biologicals are medicines which are grown and purified from large-scale cell cultures of bacteria or yeast, or plant or animal cells, and include vaccines, growth factors, immune modulators, monoclonal antibodies, as well as products derived from human blood and plasma (World Health Organization, 2024). | In contrast to the production of small molecule APIs, production of biologicals with their growth media and buffer compounds may be associated with a high environmental impact, e.g., through energy and materials use. For example, fermentation rooms are characterized by specific heating, ventilation and air conditioning requirements, which can account for up to 75% of the plant's total electricity consumption (Renteria Gamiz et al., 2019). Biobased resources require land, fertilizers and water and can result in other environmental impacts such as eutrophication and acidification (Renteria Gamiz et al., 2019), compared to the use of fossil-based materials. | |
| 5. Relocating production sites to within the EU leads to shorter supply chains, less transport emissions, and a higher percentage of renewable energy use. The energy mix in Europe (using renewable energy) is cleaner than in other continents (International Energy International Energy Agency, 2024). | When raw materials need to be transported instead of the finished API, the volume of material is much larger. If this is not possible within a geographic region, transport emissions will again increase. | Moving production to Europe may lead to a risk of trade bans and issues with diplomacy (European Commission, 2020; the White House, 2021). |
| ***Prescription and treatment*** | | |
| 6. Replacing pharmacotherapy by psychotherapy leads to less impacts on the environment through | Psychotherapy impacts the environment through the use of office space (with associated heating | An increasing number of referrals for psychotherapy may lead to longer waiting lists, |

(*continued on next page*)

**Table 1** (*continued*)

| Mitigation options to reduce environmental impact | Trade-offs | |
|---|---|---|
| | Environmental aspects | Social and economic aspects[a] |
| reduced production, distribution and release of pharmaceutical residues into the environment. Patients experiencing stress or mild symptoms associated with depression may benefit from psychotherapy as well as pharmacotherapy (Cuijpers et al., 2020). | and materials) and travel. Patient travel and staff commute are associated with considerable contributions to healthcare's emissions ( Steenmeijer et al., 2022a,b; Tennison et al., 2021). | which in turn may lead to neglected symptoms and complicated treatment. Although treatment guidelines often recommend to start with psychotherapy first (e.g., in the Netherlands; NHG, 2022), waiting lists, and costs or reimbursement rules may prevent that. |
| 7. The current anaesthetic gases are safe to patients, but they are persistent in the atmosphere, may contain PFAS moieties, and have a considerable Global Warming Potential (Anderson et al., 2021). Alternatively, intravenous anaesthesia, for example, Propofol, has a considerably lower climate impact (McGain et al., 2020). | Use of intravenous anaesthesia requires more materials and plastics entering landfills (McGain et al., 2020). Besides, intravenous anaesthesia may enter the aquatic environment after use or when discharged into sinks (Hu et al., 2021). Taking Propofol as an example, it seems that most of the active substance is metabolised into inactive conjugates (Favetta et al., 2002). However, these conjugates may form back into the active substance in the aquatic environment ( Zillien et al., 2022). | |
| 8. Patients may decide to stop treatment or lower the dose because of environmental considerations (e.g., for antibiotics or psychotherapy). | Treatment interruption may lead to additional treatment if the source of the disease has not disappeared. For example, schizophrenic patients who are not compliant with the treatment regime (treatment interruption) have a higher risk for relapse resulting in increased hospitalization, which is associated with increased energy use use (Debavaye et al., 2019). | The risk of relapse adds pressure on society and healthcare systems. |
| ***End-of-Life*** | | |
| 9. Ecodesign of pharmaceutical packaging includes the use of smaller size packaging, avoiding superfluous elements and empty spaces, which reduces material and production costs, and transportation impacts (Bassani et al., 2022). | Lightweight material can present higher life cycle impacts compared to a heavier one. For example, although blister packaging uses less material than bottles, their environmental impact is larger, mainly due to aluminium used, higher volumes of secondary packaging, and material mix which may be a challenge for recycling. Alternative materials (e.g., "biomaterials") can have higher production impacts or require additional transformation processes or end-of-life treatments (Bassani et al., 2022). | The benefits of any changes in packaging need explaining to the patient. The packaging still needs to be practical and functional, i.e., easy to open, to have a positive impact to patient adherence to their medical treatment (Shah et al., 2017; Lorenzini et al., 2022). |
| 10. Re-dispensing unused drugs within a local or hospital setting leads to a reduction in costs and reduces the environmental footprint (Smale et al., 2023). | | In a hospital setting, take-back schemes may be easily controlled and the quality of re-dispensed medicines can be guaranteed, as was shown by Smale et al. (2023) for oral anticancer drugs. However, in general pharmacies this may not be the case. Reduced quality influences patient safety. Moreover, collection boxes in public spaces that are too easily accessible may lead to issues with safety of children or others who may try to take pharmaceuticals out of these boxes (e.g., opiates), which then may lead to intoxication and hospital treatment. |
| 11. Urine bags are used to prevent emissions of X-ray contrast media into water, which leads to a lower impact on water systems and drinking water (Dekker et al., 2022). | The urine bags need to be produced and distributed, and are collected with regular waste and then incinerated. This involves the use of materials, land, and energy. | Patients need to use urine bags 3–4 times to collect X-ray contrast media. In this case, the patients are relatively healthy. A study on cytostatic drugs has concluded that for the patients using these drugs, chronic use of urine bags would not be preferred from a patient perspective as their use would be an additional burden to sick patients and because the environmental impact of these cytostatics is limited (Moermond et al., 2018). |
| 12. Advanced sewage treatment or onsite wastewater treatment at hospitals removes pharmaceutical residues, thus improving water quality. | Additional treatment steps require energy and material and still does not remove all pharmaceutical residues (Kümmerer et al., 2019). Onsite water treatment at hospitals may not be the most sustainable choice if good communal sewage treatment facilities are in place. | Ozonation, one of the most promising options for advanced wastewater treatment, causes bromate formation. Bromate is a possible carcinogenic substance to humans, and thus undesirable in drinking water sources. Removal of bromate from drinking water sources costs additional resources ( Morrison et al., 2023). In low to middle income countries water treatment may not be available. In these countries, installing sanitation, even with relatively simple techniques, will add significantly to environmental and human health. |

[a] obvious trade-offs like costs and efficacy/safety for patients are not further mentioned.

opportunities.

### 2.4. Evaluation of trade-offs

Environmental safety (lowering risks due to aquatic pollution) does not always go hand in hand with other environmental sustainability metrics. Nano-medicines may lead to less API demand and thus less pollution due to production of APIs, but some (mainly inorganic) nano-carriers will also reach the environment and will persist there (Table 1, example 1). Additionally, Table 1, example 7 shows that prevention of greenhouse gas emissions by replacing anaesthetic gas by intravenous anaesthesia may lead to an increased impact on water systems. Furthermore, a consequence of some of the discussed measures may be increased production and thus production of waste outside of the EU (Table 1, examples 2, 3 and 7).

Currently, for a value-based healthcare supply-chain, policy makers focus on patient outcomes and patient experiences with respect to healthcare costs. Less conventional values like environmental impact are often overlooked (Neumann et al., 2022). Ideally however, one should incorporate all elements of sustainability in the decision making process, including environmental sustainability, in addition to social and economic sustainability. A few pilot projects have explored the option of accounting for environmental impact in health technology assessments of new pharmaceuticals, but this merits further exploration (Toolan et al., 2023). For example, is society willing to pay for a more environmentally sustainable treatment option, especially when healthcare costs are already high (Chambon et al., 2023)? Future Health Technology Assessments (HTAs) should consider incorporating environmental impact as one of the outcomes of interest.

## 3. The way forward

There are several factors that lead to decisions in which trade-offs are not always considered, such as the lack of knowledge and awareness, and lack of data and tools. Furthermore, trade-offs are often hidden because of the complexity of the system or merely because they are dynamic in nature. The question is then if and how these should be taken into account. The EU framework of 'safe and sustainable by design' (SSbD; Caldeira et al., 2022) proposes a product or treatment should be better in at least one of the safety and sustainability dimensions without significant negative impacts in any of the other dimensions, as compared to the current default treatment. For pharmaceuticals, this is even more relevant and touches upon medical-ethical aspects: are we willing to sacrifice potential patient safety for a more sustainable treatment option, and who gets to decide (Chambon et al., 2023)? A study with gynaecology patients has shown that they are open to choose climate friendly options (Cohen *et al.*, 2025). Thus, there is a strong need for a holistic view, the use of multi-criteria decision-making tools, and clear environmental guidelines.

Once identified, information on trade-offs can also be used for targeted improvement of (environmental) sustainability. During the manufacturing phase, many direct trade-offs can be tightly controlled through good manufacturing practices. Besides this, when redesigning an API, product or treatment, or when comparing different treatment options, it is important to know what are the trade-offs, what can be solved and what cannot be solved, and how to approach this further. The question is then how far do we want and need to go? E.g., can some safety be sacrificed, how much additional cost is acceptable? In final stages where the room for improvement is rather small, large investments may be needed for relatively small or incremental additional benefits. This again underlines the importance to include this system thinking from very eary on in product development.

Our desired dot on the horizon is an assessment system, allowing stakeholders to balance environmental aspects with other (economic and/or social) sustainability aspects, depending on the stakeholders needs and wishes. This system should be based on holistic systems-thinking, identifying trade-offs as well as synergies, and could include solely environmental considerations (e.g., fitting into an existing health technology assessment) or could include also social or economic considerations. If and how these criteria should be quantified, weighed against each other and monitored should be based on scientific considerations. However, which criteria are seen as most important may also depend on ethical considerations and (inter)national or institutional policies, which vary between stakeholders. Thus, an environmental sustainability assessment system should be flexible enough to allow for this, incorporating the possibility to weigh criteria in a transparent manner.

Ideally, well informed choices are made after comparing the different sustainability aspects (environmental and/or socio-economic) of the function of a product system. By function we mean, for example, treating a patient with a certain indication to achieve health gains. To make this comparison, sustainability criteria may be applied along the whole life cycle (Fig. 1), which can be quantified in a life cycle sustainability assessment (LCSA). Combined with environmental risk assessment this can help to identify trade-offs between environmental, social and economic impacts over the life cycle, although there is no consensus on the best combination of indicators and sustainability goals (Backes and Traverso, 2022; Van Wilder et al., 2024). Using a systematic assessment method for (environmental) sustainability may help prevent burden shifting, e.g., when in a new treatment ecotoxicity is decreased but the carbon footprint increases.

Future changes may necessitate new assessments (e.g., energy use becomes less important once all energy has become renewable). Prospective LCSA, using future socio-economic scenarios (De Souza et al., 2023), can help identify potential future trade-offs. Whilst there still are shortcomings hampering the practicability, e.g., because of a lack of data, efforts are ongoing to make LCSAs operational, e.g., in the EU Horizon projects Orienting (orienting.eu) and TransPharm (transforming-pharma.eu), where the latter is specifically aimed at more environmentally sustainable pharmaceuticals.

A lack of data is currently seriously hampering the assessment of trade-offs. Complete and reliable data on environmental impact on water organisms after the use phase is only available for a couple of hundred APIs (where thousands are authorized for use worldwide), and often not easy to find (Cannata et al., 2024). Data on material and energy use, waste generation, direct emissions and production location characteristics is often not available in the public domain (Steenmeijer et al., 2022a,b). Companies need to be open and transparent regarding this information, so others are able to independently validate their life cycle assessments and can use the underlying data for their own assessments, e.g., to compare between different pharmaceutical treatments. The European Commission was recently urged to include more stringent and harmonized approach towards data availability for life cycle assessments in their new Pharmaceutical legislation (Piët et al., 2024).

Tools driven by artificial intelligence (AI) may aid in assessing sustainability of pharmaceuticals by filling data gaps, although the use of AI in itself also has a large carbon footprint (Dhar, 2020). Besides this, AI models are trained on existing data and need appropriate training and validation data as well as careful assessment of results. If this data contains systematic errors, the model will make errors in the predictions too, following the garbage in-garbage out principle (Dobbelaere et al., 2021). Hence, availability of reliability metrics for training data and predictions is a prerequisite for the implementation of AI tools. A current application of AI is the prediction of environmental data for APIs. Also in this case, molecular property prediction tools are becoming increasingly mature but their reliability might be limited by small training datasets (Walters and Barzilay, 2021). Thus, AI may be used to fill data gaps, but accurate data is still needed for training and validation. CCurrently, the use of AI to deal with data gaps is hampered by these same data gaps. Therefore, this calls for strong action towards companies to increase their transparency regarding environmental metrics.

The quantity and quality of available data will determine the success of properly identifying and considering trade-offs in decision-making, by e.g., regulators, procurement agencies and other stakeholders. This is crucial to avoid regrettable decisions, similar to avoiding regrettable substitutions of chemicals (when a chemical with an unknown or unforeseen hazard is used to replace a known problematic chemical (Maertens et al., 2021; OECD, 2021). Using a systematic assessment method for (environmental) sustainability may also help to prevent burden shifting, e.g., decreasing ecotoxicity but increasing carbon footprints, or decreasing carbon footprints due to production but increasing carbon footprints due to non-medical treatments. Furthermore, these choices should be facilitated, considering all aspects, in environmental sustainability guidelines with standardized tools and methods, including how to decide which trade-offs are most important.

When making decisions, not only facts but also emotions and perspectives may play a role (Chambon et al., 2023; Cohen et al., 2024) which could lead to an additional motivation for transitioning toward sustainable healthcare. Documentation on trade-off decisions including a justification on how trade-offs were weighed, should be transparent and publicly available to guide future decisions. Consequently, healthcare professionals and other stakeholders in the life cycle of pharmaceuticals could be able to make informed choices taking all identified trade-offs into account, also the ones that are not immediately clear in their daily practice because of different spatial and temporal scales.

Finally, it should be stressed that therapeutic freedom of healthcare professionals and patients is an important principle. Healthcare providers decide on the most appropriate therapy based on their knowledge and experience. Whereas clinical aspects, social and economic trade-offs are typically extensively discussed in e.g., HTAs and disease treatment guidelines, information on environmental trade-offs is lacking. Likewise, educational training currently often does not touch upon the environmental sustainability of medical treatment (Mattijsen et al., 2023). Thus, implementation of environmentally conscious choices in daily practice is as important as having the methodology to do so. Awareness raising and education of stakeholders in healthcare is therefore vitally important, starting with providing fact-based education modules and integrating environmental sustainability components in treatment guidelines.

## 4. Conclusion

This commentary shows that when making decisions towards more environmentally sustainable pharmaceutical treatments, trade-offs should be considered throughout the whole life cycle from production, use and end of life (See Table 2 for recommendations). Some trade-offs can be tightly controlled especially during the manufacturing phase through good manufacturing practices, leading to improved processes and synergies. However, there are many ‘hidden’ or ‘indirect’ trade-offs that can impact the environmental

**Table 2**
Recommendations on how to deal with trade-offs regarding environmentally sustainable pharmaceutical treatment.

| Recommendations |
|---|
| • All aspects along the entire pharmaceutical life cycle, from design to the waste stage, need to be considered when taking decisions to make pharmaceuticals more environmentally sustainable. Trade-offs should be systematically identified, to make informed choices and avoid burden shifting from one aspect to another. |
| • To enable quantitative comparisons between these aspects, standardized and harmonized sustainability assessments should be performed, using realistic and accurate data. This includes transparency about decisions and underlying reasoning. |
| • To prevent burden shifting from one aspect to another, life cycle sustainability assessments can be used as a component of multi-criteria decision making. |
| • To avoid regrettable substitutions, choices to replace one treatment with another should only be made if similar data are available for both options, and the alternative is clearly more sustainable over the currently used option. |
| • An assessment system should accommodate the dynamic nature of some criteria and future changes (e.g., energy use has less importance as a sustainability criterion once all energy becomes renewable). A holistic system needs to include the expertise of all stakeholders along the life cycle. |
| • Companies should provide (quantitative) data needed for regulators, procurement agencies, and health care professionals to make informed decisions. In case of data gaps, artificial intelligence methods may be used. |
| • Healthcare professionals and other stakeholders in the life cycle of pharmaceuticals should be encouraged and enabled to make informed choices and take environmental sustainability of a pharmaceutical treatment into account. |

sustainability of a pharmaceutical. Because this, stakeholders may make choices that lead to a sustainability improvement in one area, but which has considerable negative effects in another area. Tools like life cycle sustainability assessment and risk assessment should be used in a holistic manner, using multi-criteria decision-making. We argue that this should be facilitated, considering all aspects, in clear environmental sustainability guidelines for policy makers as well as stakeholders in the healthcare sector. In summary, rather than avoiding, ignoring or lamenting trade-offs, we should accept them as an inherent part of decision-making. It's crucial to approach trade-offs proactively, making choices with careful consideration, strategic thinking, and deliberate intent. The data necessary to perform these choices, should be provided by pharmaceutical companies in a more transparent, harmonized way, preferably coordinated by bodies like the European Medicines Agency or the World Health Organization.

## CRediT authorship contribution statement

**Caroline T.A. Moermond:** Writing – review & editing, Writing – original draft, Conceptualization. **Neele Puhlmann:** Writing – review & editing, Writing – original draft. **Lowik Pieters:** Writing – review & editing, Conceptualization. **Avtar Matharu:** Writing – review & editing, Writing – original draft. **Lieselot Boone:** Writing – review & editing. **Maarten Dobbelaere:** Writing – review & editing. **Héloïse Proquin:** Writing – review & editing, Conceptualization. **Klaus Kümmerer:** Writing – review & editing. **Ad M.J. Ragas:** Writing – review & editing, Conceptualization. **Rodrigo Vidaurre:** Writing – review & editing. **Bastiaan Venhuis:** Writing – review & editing. **Delphine De Smedt:** Writing – review & editing, Writing – original draft.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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## Data availability

No data was used for the research described in the article.

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