

# GREENER Pharmaceuticals for More Sustainable Healthcare

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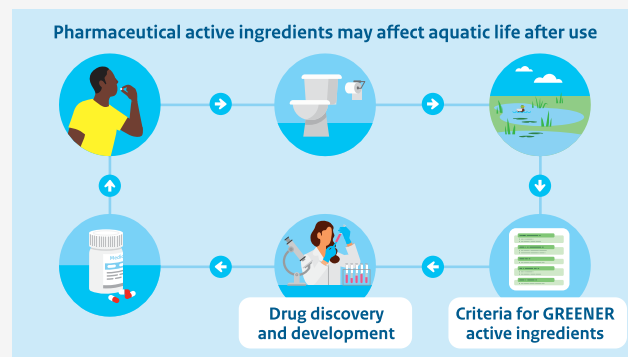
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**ABSTRACT:** Medicines are essential to human health but can also impact the aquatic and terrestrial environment after use by patients and release via excreta into wastewater. We highlight the need for a GREENER approach to identify and meet important environmental criteria, which will help reduce the impact of medicinal residues on the environment. These criteria include effect reduction by avoiding nontarget effects or undesirable moieties, exposure reduction via lower emissions or environmental (bio)degradability, no PBT (persistent, bioaccumulative, and toxic) substances, and risk mitigation. With all of these criteria, however, patient health is of primary importance as medicines are required to be safe and efficacious for treating diseases. We discuss the feasibility of including these criteria for green by design active pharmaceutical ingredients in the process of drug discovery and development and which tools or assays are needed to accomplish this. The integrated GREENER approach can be used to accelerate discussions about future innovations in drug discovery and development.



**KEYWORDS:** *pharmaceuticals, drug discovery and development, environment, sustainability, criteria, water quality*

## MEDICINES IMPACT THE ENVIRONMENT

Medicines are essential to human health, and as such, they are important in realizing the UN's Sustainable Development Goal (UNSDG) of "Good Health and Well-Being". At the same time, healthcare, including pharmaceuticals, contributes 4.4% of worldwide greenhouse gas emissions.<sup>1</sup> In addition, active pharmaceutical ingredients (APIs) themselves can also cause environmental impacts, for example, on aquatic ecosystems and drinking water resources, following patient use and downstream of production sites.<sup>2,3</sup> Thus, although medicines are essential for human health, they also impact the environment, which is also vitally important to human health,<sup>4</sup> and almost all of the UNSDGs, including "Life under Water" and "Clean Water and Sanitation".<sup>5</sup>

APIs and their metabolites enter surface water via excreta after patient use and incomplete removal by wastewater treatment plants and are detected in surface waters throughout the world, with the highest concentrations in low- to middle-income countries (LMICs) with limited sanitation.<sup>6</sup> Although the concentrations of APIs in surface water are typically nanograms per liter or less,<sup>2,6,7</sup> even at these low concentrations their presence potentially impacts aquatic ecosystems and drinking water resources. Environmental risks to wildlife are due to subtle chronic effects that can impact individual fitness and population health. Examples include histopathological changes to tissues, feminization of male fish, and behavioral changes in both fish and aquatic inverte-

brates.<sup>2,3,7–10</sup> The environment is also vitally important to human health, as reflected in the One Health approach.<sup>4,11</sup> In addition, the presence of pharmaceutical residues in sewage sludge used for fertilization and treated wastewater used for irrigation may cause uptake of these residues by crops.<sup>12</sup>

The presence of APIs, their metabolites, and their environmental transformation products in surface and ground waters has already been a growing environmental and public health concern worldwide for several decades, because of risks to ecosystems and their presence in drinking water sources.<sup>3,7–10,13,14</sup> Although in many developed countries a risk assessment must be performed for marketing authorization, an environmental risk is not a reason to refuse marketing authorization, as benefits for the patient are assumed to be more important (e.g., in EU Directive 2001/83/EC). Aging populations combined with increased accessibility to healthcare will lead to increased use of medicines, notably in LMICs. With the majority of current sewage treatment systems failing to remove all pharmaceuticals, and even more limited

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## GREENER concept for discovery and development of active pharmaceutical ingredients with less environmental impact after use

### Good practice for patients

- Well-being of the patient always comes first. This principle is often part of authorization legislation.
- Medicines are required to be safe and efficacious in treating the disease.

### Reduced off-target effects, high specificity

- The mode of action of an API should be specific, in order to reduce possible (side) effects that an API can have on patients and on organisms in the environment.
- There should be a high margin of safety between pharmacological effects and adverse effects, reducing off-target effects

### Exposure reduction via less emissions

- Reducing exposure can be achieved by less emissions after patient use.
- A possible solution is the development of new types of products such as low-dose APIs, personalized medicines, or better delivery methods to the target.

### Environmental (bio)degradability

- APIs and metabolites should not be persistent in the environment.
- They should preferably be transformed into non-persistent molecules in the sewage treatment plant or the natural environment, while still meeting stability requirements in the patient's body.

### No PBT (persistent, bioaccumulative as well as toxic) substances

- PBT substances may accumulate in food webs and could have long-term effects on ecosystems.
- When APIs meet PBT criteria, exposure reduction should be a goal.

### Effects reduction: avoid undesirable moieties

- Some APIs contain structural molecular moieties such as perfluorinated groups (e.g., PFAS) which present a potential risk to the environment.
- When designing new APIs, these molecular groups should be avoided when they are not central to the efficacy, safety and delivery of the medicine to the patient.

### Risk and hazard mitigation

- When APIs are still expected to affect the environment, options for risk and hazard mitigation should be part of further product development.
- These can be found in other parts of the pharmaceutical use chain, like prescription, use, and waste.

**Figure 1.** GREENER concept for discovery and development of active pharmaceutical ingredients with lower impact on the environment after use by patients.

sanitation and sewage treatment in LMICs, an increase in the unintended burden of human pharmaceuticals on the environment is anticipated. The UN's Strategic Approach to International Chemicals Management (SAICM) policy on Environmentally Persistent Pharmaceutical Pollutants (EPPPs) recognizes the growing problem of pharmaceuticals in the environment, which urgently needs to be addressed to protect human and environmental health worldwide.<sup>15</sup>

The ecological footprint of pharmaceuticals includes greenhouse gas emissions, consumption of energy and materials, including water and solvents in drug development and manufacture, and impacts of APIs on the environment after use.<sup>16</sup> Our focus is the latter.

### ■ WAY FORWARD: GREENER PHARMACEUTICALS

Part of the solution to the problem of API residues in the (aquatic) environment includes the design and development of APIs and other drug constituents that have less environmental

impact, either because they are intrinsically less persistent and less harmful or because their environmental risks are reduced by targeting and/or minimizing drug use and reducing emissions after use. The prerequisite for all of this is that therapeutic activity and patient safety be retained.

The intimate link between environmental and human health is now widely recognized and upheld by the One Health approach.<sup>4,11</sup> Despite this, there is currently limited interaction between environmental scientists and drug discovery and development experts on these topics. However, a reduction of the impact of pharmaceuticals on the environment can be addressed only by using a cross-sectoral approach<sup>17</sup> with the healthcare sector, environmental experts, regulators, and drug design and development experts exchanging their expertise and views on opportunities and barriers and working jointly toward possible solutions. Knowledge of environmental issues, sustainable pharmacy concepts, and relevant principles of green chemistry<sup>18–20</sup> should be integrated into appropriate phases of the existing drug discovery and development

processes.<sup>21</sup> Discovery and development of APIs and other drug constituents with minimal environmental burden after their use can be coupled with innovations in product design, drug delivery, clinical diagnosis, and treatment.<sup>19,20</sup>

The proposed GREENER concept (Figure 1), including a “benign by design” approach,<sup>19</sup> takes the natural environment as well as the patient into account. The criteria we propose to help reduce the environmental impact of APIs after the patient use phase add to the sustainability principles presented by Wynendaele et al.<sup>16</sup> and the ACS Pharmaceutical Roundtable on discovery of more sustainable drugs.<sup>22</sup>

**G: Good Practice for Patients.** A potential barrier in cross-sectoral communication and interaction is the concern that environmental issues may compromise the availability of, or patient access to, medicines.<sup>8</sup> The overall objective in drug discovery and development is to develop an API that is clinically efficacious with minimal harm to patients. Every pharmaceutical must have a positive benefit/risk regarding efficacy and safety for the patient before it can be approved for human use. The GREENER concept, based on “benign by design”,<sup>19</sup> illustrates that decision making in drug discovery and development can be beneficial for both human and environmental health when some prerequisites are met.<sup>23</sup> The overarching principle “good practice for patients” holds that protecting environmental health should not compromise patient health. Because of the intimate link between human and environmental health, it is imperative that environmental considerations be increasingly embedded within this overarching principle.

**R: Reduced Off-Target Effects and High Specificity.** Drugs should be designed so they have high specificity and efficacy for particular biological targets associated with the disease being treated. Many of these drug targets are conserved to a degree in environmental species,<sup>24</sup> in which they may elicit pharmacological responses similar to those intended in humans. Increasing drug specificity will reduce the potential for additional unintended off-target effects in wildlife, as well as in patients. Margins of safety should be maximized between pharmacological effects and adverse side effects,<sup>25</sup> not only for patients but also for environmental organisms where pharmacodynamics are less well understood. Comparative genomics should be used to identify and evaluate conservation of specific drug targets and off-targets in environmental species, to predict and avoid adverse environmental effects.<sup>24</sup>

**E: Exposure Reduction via Less Emissions.** When environmental exposure levels exceed critical concentrations for inducing an adverse effect, there is a risk to ecosystems.<sup>7–10</sup> These risks can be minimized by reducing exposure, i.e., presence of pharmaceuticals in the environment. Exposure can be reduced by minimizing emissions of APIs into the environment. This includes developing new types of products that can be administered in low doses (without having low-dose toxicity to the environment) or using drug administration methods based on more precise delivery methods like personalized medicine, antibody–drug conjugates, and nano-drug delivery systems. Targeted delivery methods, which ensure the API is directed to the target organ or physiological system effectively, can reduce the amount of API needed for efficacy and therefore the amount of API that could reach the environment. However, these approaches may provide a range of further uncertainties in terms of environmental risk and carbon footprint.

**E: Environmental (Bio)degradability.** Avoiding the development of APIs that are persistent in the environment or form persistent metabolites can also reduce exposure. Hydrophilic and persistent APIs also have the potential to end up in drinking water sources. APIs should preferably be designed to be stable enough during production, during distribution, and in the patient’s body. However, their design could also take into consideration the possibility that they may be transformed into nonpersistent molecules in sewage treatment plants and the natural environment and to allow for complete mineralization in the long term. This may seem contradictory, but in fact, a molecule’s stability depends on specific conditions such as pH, redox potential, presence of bacteria, etc., and these conditions can differ greatly between the internal environment of the patient and the external environment, e.g., sewage treatment plant, surface water, or soil. Examples of APIs that are completely (bio)degradable in the environment are summarized elsewhere.<sup>23,26</sup> The desired properties for improved environmental degradation do not have to interfere with the API’s administration to patients.<sup>23</sup> To identify environmental (bio)degradability in the drug discovery process, medium-throughput screening assays are needed.

**N: No PBT (Persistent, Bioaccumulative, and Toxic) Properties.** Substances that are PBT [persistent, bioaccumulative (often related to high lipophilicity), and toxic] may accumulate in food webs and could have long-term effects even when present in the environment at very low concentrations. In most EU regulatory frameworks, when specified PBT criteria are met, this is reason for refusal of marketing authorization or restriction of use. Within the pharmaceuticals authorization framework, this is currently not the case, as human health outcomes are more important. Bioaccumulation may also occur in patients, so addressing this issue is a common theme for both patient safety and environmental safety. Few APIs meet all three PBT criteria, but when they do, this is a concern and exposure reduction should be a goal, without compromising patient safety. As it is desirable to administer drugs orally, most of the APIs are moderately polar and water-soluble, which minimizes (bio)accumulation in the patient’s body. However, some of them, including their metabolites and environmental transformation products, may be highly polar. This makes them very mobile in the aquatic environment, which is undesirable, especially when they are also persistent and toxic at low concentrations.

**E: Effect Reduction (Avoiding Undesirable Moieties).** Some APIs may not be a risk or hazard to the environment themselves but contain specific molecular groups (moieties) that are persistent, bioaccumulative, and/or toxic to environmental organisms, e.g., persistent polyfluorinated moieties. These moieties should be avoided where feasible (or moieties with lower risk prioritized) without compromising delivery of the medicine to the drug target, its efficacy, and safety to the patient. In drug design, some structural features are essential for the pharmacological effect or needed for optimizing drug delivery, stability, uptake, and/or distribution in the body. Attention should be given to existing lists of moieties that trigger a so-called structural alert because of concerns for patient safety. When such moieties cannot be avoided, predicted risks for patients are considered when weighing efficacy and necessity against these risks. Similarly, structural features that raise environmental concerns (like moieties that do not degrade in the environment) may also be taken into

account. How this can be done will largely depend on how essential such moieties are to drug safety and efficacy. An example is the antitumor agent cytarabine, which is more biodegradable than gemcitabine and 5-fluorouracil, because it consists of only pyrimidine arabinose, whereas the other two compounds contain fluorine.<sup>27</sup>

**R: Risk and Hazard Mitigation.** There will be cases in which it is not possible to apply the criteria listed above and an API may still be predicted to pose a risk (unfavorable exposure/effect profile) or hazard (persistence or undesirable moieties) to the environment. Targeted environmental monitoring can be a step in validating risk predictions. If a risk or hazard due to use of the product cannot be excluded, options for risk and hazard mitigation should be part of further product development, like limited advertising or over-the-counter availability, evaluation of alternative treatments or administration routes, and specific waste collection systems like urine bags. An example of the latter is a pilot project on the collection of X-ray contrast media in The Netherlands.<sup>28</sup> These options should be weighed carefully against patient interests and general greener concepts (the use of urine bags to collect specific pharmaceutical residues also increases the ecological footprint due to increased material use).

In addition, general risk and hazard mitigation applies to all pharmaceuticals at different phases in the pharmaceutical use chain, from disease prevention, nonclinical interventions, improved diagnosis, and prescription (e.g., choice of medicines and prevention of poly pharmacy for elderly patients) to drug administration (e.g., adapted package size, use guidelines and information campaigns to increase prudent and responsible use of prescribed as well as over-the-counter pharmaceuticals) and drug disposal (e.g., collection schemes and guidelines not to flush unused medicines through toilet or sink). In developed countries, advanced sewage treatment can be a solution for removing APIs and other micropollutants, but this is costly, does not remove all molecules, may generate unwanted reaction byproducts of unknown toxicity, and requires increased use of energy and materials. Many of these examples are currently explored within the EU's strategic approach to pharmaceuticals in the environment and the Dutch chain approach to pharmaceuticals in the environment.<sup>13,17</sup>

## ■ IMPLEMENTATION OF THE GREENER CONCEPT

Whether and how current drug discovery and development processes can be adapted to include the GREENER concept are being investigated by a number of pharmaceutical companies, in collaboration with academia and authorities, and stimulated by, e.g., the European Commission.<sup>13</sup> Developing greener APIs will help ensure sustainable healthcare by helping to protect the environment, which is also vitally important for human health.<sup>3–5,11</sup> Dialogue is required to enable drug discovery and development experts to better understand environmental hazard and risk assessment issues. This dialogue will also enable environmental experts to better understand drug discovery and development processes.

The GREENER concept highlights the most important environmental issues to be taken into account in future drug discovery and development.

- Early drug discovery involves evaluating large numbers ( $10^4$ – $10^6$ ) of compounds in high-throughput assays and *in silico* models for potency and to prioritize compounds with drug-like properties. During this process, environ-

mental criteria may be integrated using *in silico* tools for rapid screening. After hit selection, high-throughput assays for measuring environmentally relevant endpoints may be used. Some of these tools already exist (e.g., fish cell line acute toxicity assay, OECD Test Guideline 249,<sup>29</sup> and computer models to estimate biodegradation<sup>30</sup>); others still need to be developed and/or standardized. Collaboration is needed between drug discovery experts and environmental experts to improve, adapt, design, and develop these tools.

- During the early phases of drug discovery and development, including hit selection and lead identification, attempts should be made to combine the inclusion of environmentally favorable properties in the molecular structure, while improving target specificity and selectivity. During candidate optimization, there is potential to apply medium-throughput *in vitro* assays or low-throughput *in vivo* tests to relate molecular structure to environmental fate and environmental (as well as mammalian) toxicity [e.g., fish embryo toxicity (FET) assay, OECD 236,<sup>31</sup> and FET-based endocrine assay, OECD 250<sup>32</sup>].
- Later in drug development, when the selected candidate is formulated into a drug product, there may be opportunities to refine the dose (e.g., more closely tailoring the dose to patient body weight), formulation, and delivery methods. However, once an API or a medicinal product has been further developed and progresses into clinical studies, the options to further refine the environmental profile of the API or medicinal product are very limited.

It could be beneficial to identify pressures or barriers that could hamper implementation, e.g., using the DPSIR framework (driving forces, pressures, states, impacts, and responses<sup>33</sup>). Discussions with drug discovery and development experts during interviews and a workshop suggested that a potential barrier for implementation of the GREENER concept is the impact this would have on established processes (regarding discovery and development, as well as marketing authorization), which may in turn result in more complexity and increasing costs. Given this context, it is critically important that proposed changes be justified in terms of their relevance and the likelihood that environmental impact is reduced.

A more restrictive environmental legislation could help but may be difficult for countries that do not have the resources for enforcement of environmental regulations. Pharmaceutical industry parties maintain that a more restrictive environmental legislation could be counterproductive and may have implications for patient access to medicines. Alternatively, regulatory and legal barriers could be addressed, for instance, with incentives to encourage companies to adapt their processes where feasible. Possible incentives for GREENER APIs include priority review, patent lifetime extension (due to green credentials), green labeling, and sustainable procurement mechanisms.

The barriers identified above can be diminished or even avoided if screening tools can be applied that are technically feasible to incorporate into standard drug discovery and development processes. Given the enormous number of compounds in early drug discovery, it is simply not practicable or feasible to perform complex and expensive tests on

environmental species or to determine environmental fate. The limited quantity of a drug substance available at such early stages of discovery ensures that studies that require relatively large amounts of test material are not a viable option. Therefore, environmental experts should develop robust and reliable *in silico* and *in vitro* tools for which only small amounts of the API are needed. These tools can act as surrogates for apical (population relevant) environmental endpoints quantifying chronic ecotoxicity (e.g., on growth, development, or reproduction) or environmental fate properties such as persistence and mobility. In general, these tools need to be easy to use, amenable to high and medium throughput, readily available, validated on real data, published, cost and time effective, and reliable. The predictive value (accuracy as well as precision) of assessment tools should be high, if the output is used to deselect APIs that might otherwise go forward and become clinically relevant drugs.

Sustainability, including, e.g., carbon and material footprints and environmental impacts after use, has already become part of pharmaceutical procurement processes or doctor's guidelines in a number of EU countries.<sup>34,35</sup> The ongoing industry adoption of sustainable production methods using less materials and energy (carbon footprints) is an example of industry moving in the right direction without formal regulation. Nevertheless, smaller drug companies, research institutes, and academic groups may be overburdened by incorporating environmental criteria into their drug discovery and development process. Especially for those parties, transparent and publicly available tools and models are needed to move the process forward.

## CONCLUSION

This paper provides a starting point for an urgently needed cross-sectoral dialogue between environmental experts and drug discovery and development experts in industry, academia, and authorities all over the world, to explore the feasibility of developing medicines with lower impact on the environment after use. This will not always be a straightforward process, as APIs are essential for healthcare, although some pose risks to the environment.<sup>2,3,7–10</sup> Despite the fact that persistence is unwanted in the environment, the stability of the API molecule can be an inherent characteristic of the medicine that facilitates long-term use in the patient, allows for oral-based treatment, optimizes distribution, and prolongs shelf life. In these cases, the benefits of applying the GREENER criteria have to be weighed against the impact on patient need, safety, efficacy and costs of delivering healthcare globally. In many cases, applying the GREENER concept may be beneficial to patients, companies, and the environment. Further discussion of this concept is needed among all stakeholders to ensure the achievement of a One Health approach for pharmaceutical discovery and development, in which human and environmental health are intertwined.<sup>4,11</sup>

Finally, to be able to apply GREENER criteria to drug discovery and development, it is crucial to identify suitable *in vitro* and *in silico* tools, to improve and adapt them, and to develop new suitable tools and models. Also here, drug discovery and development experts should work together with environmental experts to integrate environmental criteria within the same framework that considers clinical efficacy and patient safety criteria. The GREENER concept and these tools and models will be further developed by the PREMIER consortium, an innovative partnership of scientists, public

authorities, and pharmaceutical companies on the Prioritisation and Risk Evaluation of Medicines In the Environment,<sup>36</sup> supported by the European Commission. In addition, in summer 2022 five more large EU-funded projects on green pharmacy are due to commence.

## KEY MESSAGES

- (1) Medicines are essential to human health, but residues of active pharmaceutical ingredients (APIs) also impact the aquatic and terrestrial environment after use by patients, via their wastewater. These impacts are a growing concern for both the general public and legislators worldwide. This stems from the widespread use of APIs, with the potential to cause unintended effects in exposed wildlife and contaminate drinking water sources.
- (2) The GREENER concept is proposed for use in drug discovery and development to reduce environmental impacts of APIs and other drug constituents after patient use. It should be applied acknowledging that patient health (efficacy and safety of APIs) is of primary importance.
- (3) The GREENER concept includes criteria like effect reduction by avoiding nontarget effects or undesirable moieties, exposure reduction via lower emissions or improved environmental (bio)degradability, no PBT (persistent, bioaccumulative, and toxic) substances, and risk mitigation.
- (4) This GREENER concept is a tool to promote consideration of drug properties related to environmental risk in early drug discovery, where large numbers of molecules are screened.
- (5) While some *in vitro*, *in vivo*, and *in silico* screening methods are available,<sup>37,38</sup> some need to be adapted or developed, including high-throughput screens for early drug discovery stages. In later drug discovery and development stages, more environmentally realistic (medium-throughput) environmental fate and toxicology assessment methods are needed.
- (6) Environmental scientists and drug discovery and development experts should work together to discuss the feasibility of developing active pharmaceutical ingredients that have low impact on the environment and to collaborate in developing the drug design and assessment tools needed to do so.

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