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Perspective

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ABSTRACT

Due to the expanding and ageing world population, the importance and use of medicines is expected to increase. However, this will lead to a greater impact on the ecosystem and our health in the long term.

The concept of sustainability is rather slowly gaining traction and is currently still fragmented in the pharmaceutical field. A consortium of researchers from five European universities therefore advocates a global, systematic approach and places the emphasis on sustainability already in early stages of drug development, i.e. drug discovery. According to the researchers, the competent authorities, universities, research institutions and industrial organizations all need to take sustainability more into account. They summarized the most important opportunities on the basis of ten sustainability principles.

Medicines play a crucially beneficial role in society, and their importance and use are expected to increase due to the expanding and aging world population. The global number of older persons is projected to more than double over the next three decades. However, the increased use of medicines also heightens the environmental exposure, stressing the eco-system and adversely impacting our long-term health, e.g. due to reproductive disorders and resistance to antibiotics.

The concept of sustainability is defined in different ways according to the context in which it is used. Its definition was coined by the Brundtland Commission of the United Nations as: “Sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs.” As such, this generally accepted definition is a flag that covers many charges. Overlapping concepts such as the Sustainable Development Goals (SDGs) or the One-Health approach add to the risk of blurring the vision, although this in no way diminishes their benefits. Although the sustainability concept is contested, we cannot ignore some generally accepted basic principles: put simply, sustainability is about ensuring a good life for everyone within the planet’s boundaries [1,2]. At the same time, the so-called ‘political’ character of this concept opens up a space for a societal debate about the direction our societies should take and the choices that have to be made to achieve this goal [3]. Sustainability has thus become increasingly important, not only in Europe but gradually also worldwide. It is an enormous challenge mainly because it is a so-called “wicked” problem [4]: complex and without a finite set of simple solutions, which are moreover not true or false, but rather better or worse (Table 1).

In the pharmaceutical field, this concept is rather slowly gaining traction and is currently still fragmented. As a consortium of researchers from different European universities, we want to stand up for a global systematic approach of this “wicked” problem, followed by competent authorities as well as academic, civil and industrial organisations to take into account sustainability over the entire life cycle of a medicine. We are convinced that emphasis should be paid to

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Table 1
Ten principles of sustainability applicable in drug discovery.

1	Ecological-environmental impact (benign-by-design)
2	Medical needs
3	Green chemistry
4	Artificial intelligence and big data
5	Root cause of illness
6	Risk and decision-taking models
7	Biomarkers and bioinformatics to support precision medicine
8	Cost-effective
9	Lean discovery process
10	Responsible research and innovation

sustainability from the "cradle" (i.e. the drug discovery phase) rather than only at the later stages of product development or clinical stages (the "grave"), in line with tackling the root cause as recommended in 6-sigma lean philosophy. Of course, it is a continuous loop, where the clinical experience feeds back.

What do we consider as the most important elements of (and opportunities for) **sustainability within the drug discovery** field? In this perspective, we propose 10 elements, which are intertwined with each other, not carved in stone but rather allow reflection and discussion, leading at least in part to (more) pronounced "sustainable medicines".

1. ***Ecological-environmental impact*** ("benign-by-design" in its sensu stricto meaning [5]) as an additional decision factor in discovery (vs. the environmental risk assessment (ERA) currently mostly restricted to late development phases) should be considered in benefit–risk assessment (and hence not only efficacy-safety for currently developed human drugs).

Throughout the world, human as well as veterinary (at least equally important) pharmaceuticals of all kinds are entering and accumulating in the environment [6–8]. Today, there is increasing awareness of the impact of active pharmaceutical ingredients (API's) and their metabolites and decomposition products on the environment. It is critical to understand and predict the environmental impact of these compounds. For example, multiple thousand tons of APIs are yearly produced and with a total ocean volume of 10^9 km^3, it is clear that this cocktail of bioactive APIs is continuously entering the global (world-wide) sea at ppb levels. Diclofenac residues in cattle carcasses have been shown to kill vultures, while exposure of naproxen to light breaks down this drug into degradants that are more toxic to aquatic life than the parent drug. Once excreted, drugs or drug metabolites pass freely through wastewater treatment facilities (if available) since these aren't designed to remove pharmaceuticals.

If one looks at the environmental impact of a medicine from a life-cycle prospective [9], current medicine costs do not include the environmental burden of discovery, development, commercialisation (incl. packaging) and clinical use, which will inevitably be passed on the shoulders of the future generations if we do not include sustainability concepts in the early drug discovery phase.

In its communication "The European Union's Strategic Approach to Pharmaceuticals in the Environment", the European Commission (EC) outlined a number of actions it intends to take, including environmental aspects that EC believes should become part of medical training and professional development programs [10].

Finally, as nature is still an important source of new lead structures in contemporary drug development, responsible for more than half of the approved new medicines [11], next to the world-wide use of plant/animal materials as medicines, the preservation of global biodiversity is crucial. Using innovative tissue culture technologies can preserve the original plants from extinction, while the impact of pharmaceuticals in the environment on biodiversity (including bioremediation) is still a matter of emerging research.

2. ***Medical needs*** to focus on the important health challenges, the unmet clinical needs, i.e. life-threatening, incurable, therapy-resistant, and/or neglected diseases [12,13]. There are still an estimated 6,500 diseases with no regulatory approved therapies. Repurposing opportunities, derived from real world data and/or AI exploration, may catalyze solutions for these unmet clinical needs, and accelerate a world-wide socially just distribution of health care. What to prioritize when is obviously not a neutral choice. Always in play are other interests, responsibilities, values, power, context, etc such as the developmental status, where four categories can be distinguished based on the gross national income per capita [14] or the democracy index which roughly classifies the countries into four categories [15], types of diseases, profitability of pharmaceutical companies; etc. As such, it is also necessary to keep critically evaluating what is put on the agenda, what is decided, by whom, to what ends and with what effects.

3. ***Green chemistry*** in synthesis and analytics to reduce waste and climate change drivers. In this respect, the 12 principles of green chemistry is a broad toolkit, including concepts such as the environmental factor (known as E-factor) [16], bioconversions, flow chemistry and green analytics incl. chips & biosensors [17]. Present day synthesis produces unimaginable levels of organic waste, most being organic solvents [18]. In addition, we are consuming our limited natural resources at an alarming rate, especially endangered metals such as the platinoids that are widely used in catalysis [19]. Finally, the ecological footprint of the pharmaceutical industry is enormous, encompassing massive greenhouse gas production, e.g. generating more CO_2 than the automobile industry. This is not only an issue in large-scale syntheses, but also in the labour intensive and time consuming search for new small-molecule API's in the drug discovery phase. Current practices rarely consider these sustainability aspects in the discovery phase, as opposed to the later development phases, and then only to a limited extent. The overall effect being one best described as too little, too late. The green chemistry umbrella can obviously also be extended to include pre-formulation work and dosage form design, where synthesis and inclusion of "green" excipients should be sought.

With the increasing awareness on the environmental impact and the state of the planet, strategies to make the practice of synthetic chemistry more sustainable need to be explored. Strategies to reduce the use of solvents include flow chemistry and synthetic chemistry in water (bio-inspired synthesis). To stimulate greener synthetic chemistry, parameters have been introduced to evaluate the impact and efficiency of a reaction through chemical yield and the production of waste such as atom economy [20].

The advent of recombinant DNA technology has popularized enzymes and combinations of enzymes (guided by knowledge of biosynthetic pathways) as part of the toolkit of synthetic organic chemists and biotechnologists [21,22]. With the development of directed evolution beginning in the 1990s and more recent advances in computational protein engineering [23], limitations such as narrow substrate scope, poor stereo-, chemo-and/or regioselectivity and/or insufficient stability under operating or storage conditions may be tackled.

Recent advances in computer-aided synthesis design [24] and the expanded enzyme toolbox for biocatalysis have enlarged the potential for the construction of enzymatic cascades for the efficient, step-economic and selective synthesis of target compounds [25]. Engineering of pathways in cells as factories enables the production of complex natural products, and this is not only applicable in an industrial context [26,27].

4. Automation of drug discovery, ***artificial intelligence (AI) and big data*** to increase speed and efficiency (*e.g.* in synthesis planning as well as for the prediction of physicochemical, pharmacodynamic and -pharmacokinetic properties and therapeutic outcome), thereby reducing the number of test animals and the human and environmental burden [28].

The automation and parallelization of chemical synthesis increase speed and throughput, improve reproducibility and decrease consumption of materials. Coupled to innovative approaches in the design of new scaffolds, it opens the possibility to explore wider areas of chemical space within a given time frame compared with manual, serial compound synthesis.

Recent advances in AI have proven useful in chemical syntheses planning of non-trivial target molecules. Compound activity data in vitro, in animal models and in human patients grow at unprecedented rates, affording invaluable big data to feed deep learning (DL) strategies for activity and bioavailability prediction. DL architectures have shown particular promise in data-rich fields such as image analysis or natural language processing, and have more recently been applied for predictions of aqueous solubility of active pharmaceutical compounds [29,30]. Big data approaches are likely to play a more important role in the drug discovery toolbox of the future.

Also, big health care databases are essential tools to enhance personalized drug prescriptions and formulations. Information on pharmacogenetics and metabolomics will guide drug discovery towards a more optimal balance of risks and benefits for patients [31,32].

5. Emphasis on drugs that treat the ***root cause of illness*** (instead of symptoms), discovering disease-preventive and/or -modifying agents. A large proportion of today's drug arsenal alleviates disease symptoms rather than the underlying cause, e.g. mucolytic agents in the treatment of chronic bronchitis. Indeed, the conventional healthcare system is rather reactionary (waits until a patient gets sick and then deals with the problem), is diagnosis-focused, and still largely directed towards symptom management. To further improve clinical outcomes in our patients, future therapies should maximally target the root cause of diseases, rather than their secondary effects.

While this is well established for many infectious diseases [33], with promising new drugs (incl. vaccines) also entering the antiviral field, it is much less established in other fields. New technologies such as PROTACs (proteolysis- targeting chimeras), messenger RNA (mRNA) and CRISPR/Cas9 are expected to revolutionize therapy in the coming decades. Owing to potential advantages (to dosing, side effects, drug resistance and modulating 'undruggable' targets) over traditional occupancy-based inhibitors, protein degraders such as PROTACs that induce targeted protein degradation represent a new therapeutic modality of particular interest in oncology [34,35]. They bind to both a target protein and a ubiquitin ligase, ensuring the targeted destruction of tagged proteins and offering a more pronounced effect than traditional drugs that "only" inhibit protein activity. mRNA-based drugs are a highly appealing new class of biologics that can be used to encode any protein of interest in vivo, e.g. for prophylactic and therapeutic vaccination, but also to encode therapeutic antibodies. As technology in this field rapidly advances, also the affordability is improving [36]. The CRISPR technology even has the potential to edit genetic mutations at will, curing the disease caused by such mutations (e.g. tumours, cystic fibrosis).

6. ***Risk and decision-taking*** models in drug discovery: optimal sustainable decisions taking the complete life cycle into consideration ("from cradle-to-grave/cradle"). While the predominant paradigm in drug discovery consists of identifying/designing selective ligands for a specific target, currently, important progress in understanding how these ligands modulate cellular networks (Quantitative Systems Pharmacology) is expected to improve the translation of preclinical discoveries into clinic benefits [37]. New (computational) approaches such as sustainability metrics are anticipated to guide critical path decisions. Additionally, and more broadly, social concerns are also taken into account (see element 8) and the precautionary principle should weigh heavily at environmental and health decision-making (e.g., in relation to new technologies - see element 5).

7. Use of ***biomarkers*** and ***bioinformatics*** to support precision medicine, reducing ineffective medicine use, burdening patient, society and environment. An accurate (and preferably molecularly confirmed) and rapid diagnosis, including for example the identification of disease-causing gene mutations, will improve therapy-, cost- and eco-effectiveness of medicines. The drug discovery phase should incorporate genetic and metabolomic biomarkers that can be used to stratify patients according to disease risk and optimal drug therapies. This phase should also consider drug non-adherence, as this leads to inefficient use of medicines. Such non-adherence to drugs, but also to vaccines, may compromise the fight against world most deadly diseases such as TB, corona and malaria [38]. Therapeutic drug monitoring of drug metabolites and recent advances in adherence enhancing devices, incl. smart drug delivery and accessory devices, may increase the optimal use of drugs.

8. ***Cost-effective***: as medicines are a crucial part of the health system, social justice is translated to equal access to medicines. This encompasses transparent cost-profit and efficacy discussions [39,40] leading to societally-acceptable prices, supported by adjusted reimbursement, intellectual property regulations [41], and the related regulatory data protection and market exclusivities currently applicable to support certain developments, such as repurposing. The life cycle of a medicine, with its variations and extensions, needs to be profitable, risk-covering, but fair and acceptable to society. Organisational models as well as the societal-political environment will influence the price. While the direct discovery costs are only a small part of the medicine price, this initial discovery phase ultimately determines the price.

9. ***"Lean" discovery***: to discover the right medicine in a fast, efficient and value-creating way, with optimal experimental designs [42], guided by principles to increase the confidence in the discovery conclusions such as the reproducibility principles described by Begley [43]. While the medicine development process is supported by numerous guidelines, drug discovery is (surprisingly) largely unregulated, despite its enormous importance for the success of the drug development and life cycle. To find the currently best possible treatment for a disease, it is essential that scientists and stakeholders define relevant questions and needs seek the best possible answers, taking into account different time scales (short and long term), spatial scales (from regional to global) and different concerns (see all other elements). The right questions need to be answered in a logical order, so that the drug selection process is as efficient and sustainable as possible.

10. Sustainability by ***responsible research and innovation***: novel technologies and prophylaxis/treatment principles are crucial as one of the reasons of the decreased drug discovery productivity is the increased difficulty (and costs) in finding (and validating) novel therapeutic targets. Research institutions and universities are often involved in the identification of new drug targets and hits, which ultimately may lead to an industrially developed and marketed medicine. Hence, the academic sustainability position is important, *i.a.* in the contractual translation of their findings towards industrial development and commercialization through spin-offs or external partners [44]. Finally, the government, representing society, is expected to support and stimulate innovative and sustainable research, but also to assure adequate and open deals for equitable access to compensate for its investment.

It is clear that the pharmaceutical industry will need to consider these aspects from the early life of a potential medicine. The global sustainability evaluation must become a mandatory and significant part of the "efficacy-risk" balance in the authorisation of medicines by the competent authorities, also for human medicines for which the environmental risk assessment is now not even a decision criterion in the approval of a marketing authorisation. Finally, the academic institutions also have a responsibility to include the above mentioned sustainability aspects into the curricula of undergraduate and graduate education in drug discovery.

Finding adequate treatments against unmet disease conditions, for everyone, everywhere, at a fair price, while respecting the environment and eco-systems is indeed an enormous challenge, and one that we must be better prepared for.

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Evelien Wynendaele: Conceptualization, Writing - review & editing. **Christophe Furman:** Conceptualization, Writing - review & editing. **Bartosz Wielgomas:** Conceptualization, Writing - review & editing. **Per Larsson:** Conceptualization, Writing - review & editing. **Eelko Hak:** Conceptualization, Writing - review & editing. **Thomas Block:** Conceptualization, Writing - review & editing. **Serge Van Calenbergh:** Conceptualization, Writing - review & editing. **Nicolas Willand:** Conceptualization, Writing - review & editing. **Michal Markuszewski:** Conceptualization, Writing - review & editing. **Luke R. Odell:** Conceptualization, Writing - review & editing. **Gerrit J. Poelarends:** Conceptualization, Writing - review & editing. **Bart De Spiegeleer:** Conceptualization, Writing - review & editing.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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