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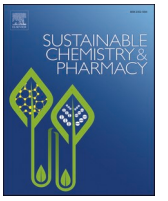

Applicability of the European Commission's framework on *safe and sustainable by design* to the pharmaceutical sector

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ABSTRACT

The chemical sector contributes significantly to anthropogenic impacts on planetary health. Thus, there is a need for a green transformation. The same holds for the pharmaceutical sector. To assist with this transformation, European Commission's Joint Research Centre (JRC) developed a framework on *Safe and Sustainable by Design* (SSbD) for chemicals and materials ("SSbD framework"). The general structure of the SSbD framework leaves room for sector-specific priorities and practices. This study explores the applicability of the SSbD framework to the pharmaceutical sector; more specifically to the development, production and use of Human Medicinal Products (HMPs). We show that the stage-gate process in R&D of HMPs fits very well with the design-assessment process of the SSbD framework, making the framework conceptually applicable to pharmaceutical R&D. Future efforts should focus on the development of i) methods to predict environmental safety and sustainability based on the limited data available during R&D, ii) a pragmatic procedure integrating SSbD into HMPs innovation, and iii) a weighing system considering also environmental safety and sustainability parameters alongside patient safety and medical efficacy. Although the assessment phase of the JRC's SSbD framework has specifically been developed for innovation purposes, we propose an expansion of its scope to pharmaceutical products already on the market. The reason is its applicability by healthcare actors to guide safer and more sustainable choices regarding the use of marketed HMPs. We call this approach *Safe and Sustainable by Comparison* (SSbC) and show that the assessment principles of the SSbD framework can be applied to SSbC.

1. Introduction

The pharmaceutical sector has been gaining attention due to its impact on the environment, for example its contribution to climate

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Abbreviations

API	Active Pharmaceutical Ingredient
CMR	Carcinogenic, Mutagenic, Reprotoxic
CSS	Chemicals Strategy for Sustainability
DMTA	Design-Make-Test-Analyze
EC	European Commission
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FLASC	Fast Life Cycle Assessment of Synthetic Chemistry
HMP	Human Medicinal Product
JRC	Joint Research Centre of the EC
LCA	Life Cycle Assessment
OECD	Organisation for Economic Co-operation and Development
PBT; vPvB	Persistent, Bioaccumulative and Toxic; very Persistent and very Bioaccumulative
PGEU	Pharmaceutical Group of European Union
PMI	Process Mass Intensity
PMT; vPvM	Persistent, Mobile and Toxic; very Persistent and very Mobile
R&D	Research and Development
SSbC	Safe and Sustainable by Comparison
SSbD	Safe and Sustainable by Design
SVHC	Substances of Very High Concerns
WWTP	Wastewater Treatment Plant

change, resulting in a push towards sustainability transformation (cf. "Pharmaceutical Strategy for Europe"; EC, 2020b). Healthcare accounts for around 5% of the worldwide greenhouse gas emissions (Belkhir and Elmeligi, 2019; Health Care Without Harm, 2019; Romanello et al., 2022). Additionally, large amounts of waste are created during pharmaceutical production (Budzinski et al., 2019) and by single use products such as syringes (EU, 2020; Health Care Without Harm, 2020). Another example relates to the environmental pollution due to the production and patients' excretion of pharmaceutical ingredients, and subsequent ecotoxic effects on environmental species and biodiversity, mainly but not exclusively due to the intended therapeutic effect (e.g., of hormones or anti-neoplastics) (aus der Beek et al., 2016; Kidd et al., 2007; Miller et al., 2018; OECD, 2019; Tyler and Goodhead, 2010; Wilkinson et al., 2022; World Health Organization, 2017).

The European Green Deal aims to transform the EU into a sustainable economy and society (EC, 2020c). To contribute to the Green Deal's ambitions, the European Commission (EC) published a Recommendation to establish a framework on *Safe and Sustainable by Design* (SSbD) (EC, 2022). Such a framework, based on the Technical Report developed by the JRC (Caldeira et al., 2022; in the following "SSbD framework"), should stimulate the (re)design towards safer and more sustainable chemicals and materials (EC, 2022) while avoiding regrettable substitutions (Maertens et al., 2021). The recommended SSbD framework consists of two components: a (re) design phase and an assessment phase. These two components are iterative and interlinked along the entire innovation process. The assessment evaluates safety and sustainability of a chemical or material throughout its entire life cycle. The safety aspects are assessed for both humans and the environment. Environmental sustainability is assessed by means of a Life Cycle Assessment (LCA) (Caldeira

Terminologies according to the SSbD framework and the Chemicals Strategy for Sustainability (CSS)

Sustainability and Safety acc. to the SSbD framework (page 2):

"When applied in the context of chemicals/materials, the concept of sustainability could be formulated as the ability of a chemical/material to deliver its function without exceeding environmental and ecological boundaries along its entire life cycle, while providing welfare, socio-economic benefits and reducing externalities. The safety concept is transversal to all sustainability dimensions (environmental, social and economic) and it is related to the absence of unacceptable risk (in line with REACH art 68 (EU, 2006)) for humans and the environment [considering exposure], preferably ensured by avoiding chemicals with intrinsic hazard properties."

Safe and Sustainable by Design (SSbD) acc. to the CSS (EC, 2020a):

"At this stage, safe and sustainable-by-design can be defined as a pre-market approach to chemicals that focuses on providing a function (or service), while avoiding *volumes* and chemical properties that may be harmful to human health or the environment, in particular groups of chemicals likely to be (eco)toxic, persistent, bio-accumulative or mobile. Overall sustainability should be ensured by [significantly] minimizing the environmental footprint of chemicals in particular on climate change, resource use, ecosystems and biodiversity from a life cycle perspective."

et al., 2022).

In view of the large environmental impact of the pharmaceutical sector, application of the SSbD framework to this sector is of crucial importance to increase its safety and sustainability (EC, 2020b). Since the structure of the SSbD framework is general in nature to be applicable to the entire chemical sector, including the pharmaceutical sector, translating the SSbD framework into sector-specific guidance is a step forward in the operationalization of the SSbD framework. It requires consideration of the characteristics of each sector, for instance the structure and complexity of the product life cycle, type(s) of use, possible innovations, the applicable design principles, and the relevance of the assessment criteria.

In the EU, current safety assessment for the Research and Development (R&D) of Human Medicinal Products (HMPs) focuses on patient safety. The assessment of patient safety is performed within the marketing authorization procedure, where patient risks are balanced against the benefits of the medical treatment (so-called benefit/risk analysis) (EC, 2023). However, as this safety assessment concerns only the patient, other human health risks, for instance *via* environmental exposure (drinking water, antimicrobial resistance) or occupational risks during production, are not taken into account. There is only a narrow focus on Environmental Risk Assessment (ERA). The ERA is part of the marketing authorization procedure, but for HMPs this is currently not part of the benefit/risk analysis. Thus, it cannot result in "no authorization" (EC, 2004; EMA, 2024). The ERA focusses solely on assessing ecotoxicological risks of the active ingredient for environmental species after use (i.e., excretion by patients). Wider sustainability aspects such as greenhouse gas emissions or resource, water and land use, or social standards are not part of the EU authorization dossier of HMPs, and they have up to now seldom been performed and published for HMPs (Hernandez et al., 2023).

The aim of this paper is to explore the applicability of the SSbD framework to the pharmaceutical R&D process, and to support the green transformation of this sector by providing recommendations for implementation. Experts from the pharmaceutical sector can decide whether and how to take them into consideration. For this purpose, we reviewed the SSbD framework itself and its accompanying documents, as well as scientific publications on the R&D process, the life cycle of HMPs, and approaches to make HMPs environmentally friendlier. The focus was on safety and the environmental dimension of sustainability of HMPs, while social and economic aspects – part of overall sustainability and therefore of SSbD – are not covered in this article as they are less mature in the SSbD framework (in terms of method development). The entire HMP is addressed, which consists of numerous ingredients including the Active Pharmaceutical Ingredient (API) and excipients needed for pharmaceutical formulation, as well as materials for its administration (e.g., syringes).

The next two sections (**Sections 2** and **3**) provide an overview of the R&D process of HMPs and the structure of the SSbD framework, respectively. Building upon this background, **Section 4** proposes a structure of the SSbD framework adjusted for the specific context of HMPs (re)design. A special focus is on the application of the SSbD principles and the safety and sustainability assessment within the R&D of HMPs. **Section 5** explores further application possibilities of the safety and sustainability assessment that may guide decision-making at several life cycle stages of the marketed HMP in favor of a safer and more sustainable option. We call this approach *Safe and Sustainable by Comparison* (SSbC). In **Section 6** and **7** we discuss implications for the pharmaceutical sector and conclude recommendations on how to move towards the application of SSbD and SSbC in the pharmaceutical sector.

2. The R&D process of HMPs

R&D of HMPs consists of a drug discovery phase and a product development phase (**Fig. 1**), which aims for an HMP that is effective and safe for the patient. For this purpose, drug discovery starts with the screening of thousands or millions of different chemical structures to identify, select and optimize compounds with the desired on-target activity (so-called hits). During lead selection and optimization, lead structures are selected out of the pool of optimized hits, again further optimized or filtered out at each gate of a screening cascade (a go/no-go decision point; Cooper, 2010). These steps result in the API candidate selection (Blass, 2015).

In silico predictions and simple, rapid high-throughput tests with a limited level of detail are used for early stages, such as hit selection. Later in the process, screenings become more refined, requiring more time and test material. In product development, i.e., preclinical and clinical studies, the selected API candidate is formulated and tested using more complex animal and human studies on

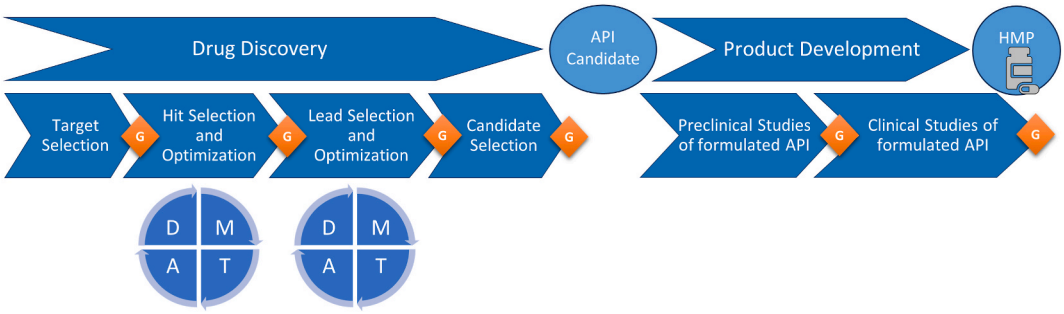

Fig. 1. The generic Research and Development (R&D) process of Human Medicinal Products (HMPs) consisting of drug discovery and product development (inspired by Messinger et al., 2016). Orange gates mark go/no-go decisions. The process is not linear as exemplified by the Design-Make-Test-Analyze (DMTA) cycle in hit and lead optimization. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

efficacy, safety and toxicology. In parallel, the API synthesis process is optimized and scaled-up, for instance, towards high product yields, volume and time efficiency of the utilized reactors, and low material and environmental costs (Dach et al., 2012). Although the R&D process looks linear, it rarely is in practice (Gyurjyan et al., 2017). For example, during hit and lead optimization multiple parameters are optimized in parallel *via* the so-called Design-Make-Test-Analyze (DMTA) cycle, where structural analogues are designed, synthesized (make), tested and results analyzed to determine whether structural changes are kept, developed further or discarded (Blass, 2015).

In recent years, environmental considerations have become part of the R&D process in some companies. This mainly concerns the application of the 12 principles of green chemistry to synthesis (Bryan et al., 2018), including the selection of materials and solvents, and the use of bio-based building blocks (Anastas and Zimmerman, 2007; Kar et al., 2022). Besides greener synthesis, there is also an increasing interest of the pharmaceutical industry in the design of greener APIs (Moermond et al., 2022; Puhlmann et al., 2024; Vidaurre et al., 2024).

3. Goal and structure of the SSbD framework

The SSbD framework has the goal to support chemical product innovation by integrating a safety and sustainability assessment in the current R&D practices, by considering a holistic and comprehensive evaluation of the (re)designed chemical or material. The SSbD framework follows the stage-gate method (Cooper, 2010) which represents the innovation process in (re)design stages from idea to launch (i.e., idea generation, idea scoping, build business case, development, testing & validation, and launch) (Cooper, 2010). As a consequence, the implementation of the SSbD framework is iterative, and at each "stage" iterations include (1) the application of (re) design principles and (2) the safety and sustainability assessment that aims to support the final go/no-go decision at the "gate".

The application of (re)design principles aims to steer the innovation process towards safer and more sustainable alternatives. The SSbD framework identifies eight (re)design principles and associated indicators to evaluate them (**Table 1**). The proposed SSbD principles relate to issues such as the selection and reduction of raw materials, the improvement of process efficiency and consumption, and the avoidance of hazardous emissions. Additional sector-specific principles can also be considered.

The safety and sustainability assessment in the SSbD framework is split into 5 steps.

Step 1: Hazard assessment of the chemical/material.

This Step looks at the intrinsic properties of the chemical/material to verify its inherently hazardousness. The SSbD framework lists three criteria which mostly refer to existing European laws and initiatives on i) most harmful substances, ii) substances of concern, and iii) other hazard classes such as acute (eco)toxicity. The criteria aim to ensure that the most harmful chemicals/materials are excluded

Table 1
The eight SSbD principles taken from the SSbD framework (Caldeira et al., 2022, chapter 4). PMI = Process Mass Intensity; SVHC = Substances of Very High Concern (Definition, REACH directive, Art. 57 a-f); CMR = Carcinogenic, Mutagenic, Reprotoxic; PBT = Persistent, Bioaccumulative and Toxic; vPvB = very Persistent and very Bioaccumulative; M in PMT and vPvM = Mobile.

SSbD principle		Definition	Examples of indicators
1	**Material efficiency**	Pursuing the incorporation of all the chemicals/materials used in a process into the final product or full recovery inside the process, thereby reducing the use of raw materials and the generation of waste.	• E-factor/PMI • Purity of recovered solvent (%) determining reusability • Water consumption
2	**Minimize the use of hazardous chemicals/ materials**	Preserve functionality of products while reducing or completely avoiding the use of hazardous chemicals/materials where possible.	• Classification of SVHC, (CMR, PBT, vPvB and equivalent level of concern having probable serious effects to human health and/or the environment) • Biodegradability (to avoid PBT, vPvB, PMT, vPvM)
3	**Design for energy efficiency**	Minimize the overall energy used to produce a chemical/ material in the manufacturing process and/or along the supply chain.	• Energy consumption • Energy efficiency
4	**Use renewable sources**	Target resource conservation, either *via* resource closed loops or using renewable material/secondary material and energy sources.	• Recycled content • Bio-based resources • Renewable energy
5	**Prevent and avoid hazardous emissions**	Apply technologies to minimize and/or to avoid hazardous emissions or pollutants in the environment.	• Biological Oxygen Demand • Amount of hazardous waste
6	**Reduce exposure to hazardous substances**	Eliminate exposure to chemical hazards from processes as much as possible. Substances which require a high degree of risk management should not be used and the best technology should be used to avoid exposure along all the life cycle stages.	• Same as SSbD principle 2
7	**Design for end-of-life**	Design chemicals/materials in a way that, once they have fulfilled their function, they break down into products that do not pose any risk to the environment/humans. Design for preventing the hindrance of reuse, waste collection, sorting and recycling.	• Recyclable • Durability • (Eco)toxicity of metabolites and transformation products
8	**Consider the whole life cycle**	Apply the other design principles thinking through the entire life cycle, from supply-chain of raw materials to the end of the product life	• Material circularity indicator • Biodegradability

during early R&D.

Step 2: Human health and safety aspects in the chemical/material production and processing phase.

This Step evaluates occupational safety over the entire life cycle of the chemical/material except the use phase (see Step 3). Environmental safety is also included, covering (eco)toxic impacts during these life cycle stages (i.e., manufacturing and processing of the chemical/material and its end-of-life).

Step 3: Human health and environmental aspects in the final application phase.

This Step focuses on the assessment of human health and environmental safety aspects related to the final application of the chemical/material.

Step 4: Environmental sustainability assessment.

This Step assesses environmental sustainability of the chemical/material by means of LCA. LCA evaluates the impacts related to the chemical/material along its entire life cycle, from the raw materials extraction to end-of-life. Environmental impacts in LCA are divided into several impact categories. The SSbD framework recommends the 16 impact categories of the Environmental Footprint method (EC, 2021), and clusters them into 4 groups: toxicity, climate change, pollution, and resources. Specifically to the toxicity group, Step 4 complements the human health and environmental risk due to chemical exposure performed in Step 2 and Step 3.

Step 5: Socio-economic sustainability assessment.

This Step includes the social and economic assessment of the chemical/material by considering its entire life cycle.

For each step, the SSbD framework aims to propose assessment criteria, as well as a scoring system to support the evaluation. Currently, criteria have been proposed for Steps 1 and 4, while criteria for Steps 2 and 3 are still under development. For instance, cut-off criteria on Step 1 are defined for the most harmful substances. Different methodologies are proposed for the aggregation of the scores of each indicator to facilitate decision-making. Step 5 is still underdeveloped in view of the limited level of implementation and methodological maturity.

4. SSbD framework applied to the (re)design of HMPs

The following subsections explore the application of the SSbD framework to the pharmaceutical R&D process. First, we define the scope of the SSbD framework in the context of HMPs, then we propose a structure of the SSbD framework adjusted to HMPs, including which SSbD (re)design and assessment steps to apply at which stage of the R&D process.

4.1. Scope of the SSbD framework for HMPs

The SSbD framework may be used to assess the overall safety and sustainability of an HMP by (re)designing i) an ingredient or the HMP itself (molecular or product (re)design), or ii) the synthesis route or another HMP-related process (process (re)design). The former (i) may be needed when, for instance, an API is persistent in the environment, especially if it is also toxic to environmental organisms. In this case, the (re)design for (complete) environmental biodegradation might be explored. The drug product may also be (re)designed, for instance by using precision delivery systems that need less API. A special case of the product (re)design is the (re) design of the application route, which may become relevant, for instance, to lower the carbon footprint by switching from intravenous to oral administration (Eii et al., 2023). Process (re)design (ii) refers to process improvement, for example, to optimize resource consumption or process efficiency. For instance, production processes that use many intermediates, many sequential production steps or much solvent may be (re)designed using other catalysts, fewer synthesis steps, less energy or flow chemistry (Michałek et al., 2022).

The aim of SSbD should be to improve some safety and sustainability aspects in parallel while avoiding a worsening of others. Thus, the implementation of the SSbD framework should result in the identification of trade-offs and evaluation of the overall improvement. For instance, novel delivery methods may consist of nanomaterials that can reduce the amount of API ending up in the environment (Jung et al., 2021; Krishnan et al., 2023). However, certain nanomaterials may also impact the environment, due to environmental persistence or the use of non-renewable resources for their production (Bundschuh et al., 2018).

In the case of redesigning existing HMPs, available information (e.g., related to the function or the environmental fate) can be used as a starting point for the redesign. This advantage is also described in literature comparing the redesign with the *de novo* design approach in the context of the *Benign by Design* concept (Lorenz et al., 2021). Furthermore, there are several examples in literature for redesigned APIs towards less environmental persistence and marketed APIs being readily environmentally biodegradable even without intentional design (Puhlmann et al., 2021). These examples show opportunities as well as barriers for further development. For example, the beta-blocker propranolol and the antibiotic ciprofloxacin were (re)designed to 4-hydroxy-propranolol and Cip-Hemi, respectively, both of which are less persistent in the environment, but still have a similar efficacy. This leads to the opportunity of lower environmental concentrations (Leder et al., 2021; Rastogi et al., 2015). In future, the overall safety and sustainability profile, including the environmental impact of the production (i.e., synthesis of environmentally better degradable APIs or excipients, Bading

et al., 2024), should be assessed to determine whether the improvement of biodegradability results in a better overall environmental profile of these alternatives compared to the original compounds.

4.2. Structure of the SSbD framework for HMPs

The iterative procedure between the (re)design and the assessment phases of SSbD is applicable to the stages of pharmaceutical R&D. This is nicely exemplified by the optimization phase of pharmaceutical R&D through the DMTA cycle (**Fig. 1**). The (re)design phase of the SSbD framework is comparable to the D (Design) of DMTA where design principles are considered. The assessment phase in the SSbD framework is similar to the A (Analyze) of DMTA, requiring also preceding M (Make = synthesizing, or at least defining the molecular structure) and T (Test = producing results, used for subsequent assessment/analysis by *in vitro* or *in silico* tools). The result of the assessment informs the next design phase. When applying SSbD to R&D, the main changes would concern additional design principles and SSbD assessment criteria to be included in the evaluation, for a more comprehensive assessment. For example, environmental risks after the use of HMPs should be assessed, as well, in addition to patient safety.

The four safety and sustainability assessment steps of the SSbD framework (see **Sections 3**) are aligned and finetuned according to the life cycle of the HMPs. The life cycle of HMPs includes the production of precursor chemicals, API synthesis, formulation of the product, packaging, distribution and sales, the use and end-of-life (Siegert et al., 2019; van Wilder et al., 2024). The R&D stage itself is not part of the life cycle in the context of SSbD because the assessment of impacts along the life cycle is ex-ante/prospective, i.e. assessing a product under development assuming it is on the market. The end-of-life includes the patients' excretion of the pharmaceutical ingredients (in original or metabolized form), emissions directly to the environment or to Wastewater Treatment Plants (WWTPs) and from that to the environment, and disposal of unused and expired products but also materials used to administer the product (**Fig. 2**, grey boxes). The unused fraction of the sold product can be disposed properly *via* collection systems (in some countries *via* domestic waste) or improperly *via* the toilette or sink.

Based on the above, **Fig. 2** shows the alignment of the four assessment steps of the SSbD framework to the HMP life cycle. Step 5, the socio-economic sustainability assessment, is out of the scope of the present manuscript. Below, a description of each step is provided.

- Step 1 is based on the hazard properties of all ingredients. For HMPs this includes the API and the excipients.
- Step 2 considers occupational and environmental safety during all life cycle stages related to the production of the HMP from "production of precursor chemicals" to "distribution and sales". In contrast to the SSbD framework, this Step excludes occupational safety during the "end-of-life", which is instead included in the following Step 3. According to the JRC, the "end-of-life" stage would be considered also in Step 2, and not in Step 3, if there is occupational exposure (e.g., during waste treatment). However, we include all different end-of-life scenarios in Step 3 independently on potential occupational exposure. The reason is that HMP's end-of-life with or without occupational exposure is rather unpredictable during the innovation phase. For example, it is region-dependent whether and how the wastewater is treated. Same holds for collection systems of unused HMPs. However, R&D of HMPs is a global business, not aiming for a specific region (market).
- Step 3 considers human and environmental safety during the use of the HMP, including potential professional use (defined under the REACH regulation), and during HMP's "end-of-life". Considering that there is a worldwide high percentage of non-treated wastewater that enters the environment directly (i.e., no WWTP installed, UN Water, 2017) highlights the need of assessing the environmental safety in both scenarios, i.e., with and without wastewater treatment. There are limitations for the assessment of safety at HMP's end-of-life during the innovation process because of lacking information on risks by the cocktail of compounds occurring in WWTPs and the environment.
- Step 4 covers all stages of HMP's life cycle, accounting for the materials, energy, and water consumption, and for the emission to water, air, and soil that would lead to an environmental footprint.

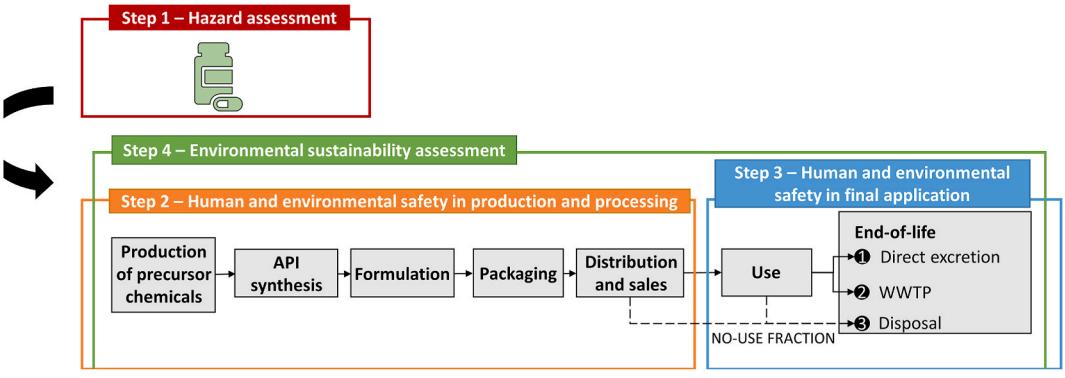

Fig. 2. Alignment of the assessment Steps 1–4 of the SSbD framework to the life cycle stages of a pharmaceutical product from the production of its precursor chemicals to its end-of-life. The alignment informs the scope of the assessment steps during the pharmaceutical R&D.

The application of the two components of the SSbD framework (i.e., (re)design principles and assessment phases) were combined with the current R&D process of HMPs, suggesting when which (re)design principle and which assessment step become relevant (**Fig. 3**). The next subsections describe how the implementation of the SSbD framework and the current R&D process have been combined. The stage-gate approach aligned between the current R&D of HMPs and the SSbD framework implies that information on product properties, performance, and thus on safety and sustainability, will become increasingly available throughout the innovation process. The increasing level of complexity and data availability can be considered during the sequential development of the assessment steps of the SSbD framework when applying it to R&D (Abbate et al., 2024).

4.2.1. SSbD principles applied to the R&D of HMPs

The eight (re)design principles of the SSbD framework (**Table 1**) are applicable to different stages of the pharmaceutical R&D process (**Fig. 3**, upper part). To decide at which stage(s) the principles can be applied we considered a) which properties of the HMP or its processing (e.g., use of raw materials, generation of waste) are addressed by the different (re)design principles and b) at which R&D stage(s) knowledge about these properties is likely to be available (**Table 2**). For example, to apply design principles to the synthesis of the API, the API itself needs to be defined already. In general, the design principles should be applied as early as possible to enable an appropriate consideration.

We found that principles related to hazard and end-of-life design are applicable to the molecular design and selection of API candidates, as well as to scaling-up the API synthesis regarding all raw materials needed (solvents, reagents, catalysts, etc.). These principles can also be applied to formulation development and the excipients needed when moving towards product development (**Table 2**, R&D stages nr. 1). Design principles regarding greener processes (efficiency, renewables) can be considered during the development stages (**Table 2**, R&D stages nr. 2). An evaluation of the complete product, including the API, excipients, application methods, and packaging, is only possible at the final stage of development (**Table 2**, R&D stages nr. 3). For instance, the packaging has to be evaluated (considering the material itself) and the packaging size is based on the projected use and regulations, both of which affect the quantity of HMPs produced, sold, used and potentially disposed (e.g., due to expiry).

Indicators can be derived from the general SSbD principles to guide the pharmaceutical innovation process, even if a complete safety and sustainability assessment is not yet possible (**Fig. 3**, lower part) (Ang et al., 2021; ACS GCI Pharmaceutical Roundtable). Especially for SSbD principle 1, many indicators are known. Examples are mass metrics, such as atom economy, the E-factor, green aspiration level, and Process Mass Intensity (PMI) (explained by Martínez et al., 2022). These indicators inform about sustainability parameters such as resource efficiency and amount of waste (Martínez et al., 2022). They have different pros and cons, but overall mass metrics are useful indicators for the environmental footprint of a chemical's synthesis pathway, and can be useful to identify potential environmental sustainability hotspots already when selecting synthesis routes. Pharmaceutical companies already use mass metrics for SSbD principle 1 as well as the solvent guide on hazards for SSbD principles 2 and 6 (Ang et al., 2021; ACS GCI Pharmaceutical Roundtable).

4.2.2. Safety and sustainability assessment

The assessment should evolve along the entire pharmaceutical R&D process (**Fig. 3**, lower part). As proposed by the JRC, the different assessment steps do not have to be performed sequentially. The order and also the option for parallelism depend on the design process and the information availability (Abbate et al., 2024). This is in line with the flexible and agile nature of the R&D process (Berggren et al., 2018; Puhlmann et al., 2024). To decide when the assessment steps may become relevant during R&D we compared a) the available data for each step along the innovation with b) identified SSbD assessment endpoints that are covered already in or are new to R&D (**Table 3**). For example, assessing greenhouse gas emissions during production of the API is possible only after a potential synthesis route has been defined which usually takes place in parallel to preclinical studies.

The applicability of the assessment steps to pharmaceutical R&D is summarized in **Table 4**. Assessment criteria for human safety (part of Steps 1–3) are already considered in pharmaceutical R&D by default. However, this is limited to the patient and not *per se* the human population through the environment (e.g., consumption of drinking water or fish) or the workforce at production facilities. However, occupational health and safety legislations apply in API plants leading to first considerations in R&D (European Chemicals Agency, 2017). Nevertheless, many assessment endpoints of environmental safety and sustainability are new endpoints, usually not considered in the current R&D process. Safety during production (part of Step 2) can be considered at the earliest during synthesis route selection and upscaling (i.e., during product development). Performing Steps 3 and 4 as early as possible calls for simplified methods, for example simplified LCA as Step 4 might require data and information that will be collected beyond the innovation process, such as electricity or water consumption for HMP's production.

5. Expanding the scope of the SSbD framework's assessment to Safe and Sustainable by Comparison (SSbC)

Stakeholders in the healthcare sector often voice the wish to become more sustainable (Heni et al., 2023). They ask for a system to compare different APIs or HMPs, enabling them to choose the most sustainable treatment option or to assess whether a non-medicinal treatment is more environmentally sustainable. For instance, choices between medicinal and non-medicinal treatment are options for treatment of mild depression (psychotherapy instead of antidepressants) or muscle issues (physical therapy instead of Non-Steroidal Anti-Inflammatory Drugs, NSAIDs). Stakeholders often state that a choice for an environmentally safer or more sustainable option can only be made, if efficacy and safety of the treatment and ease of use are not compromised (Heni et al., 2023). Cohen et al. (2024) advocate for integrating individual considerations, societal responsibilities and systemic changes to promote environmentally sustainable healthcare. The driver is the direct connection between environmental hazards and patients' well-being (Cohen et al., 2024).

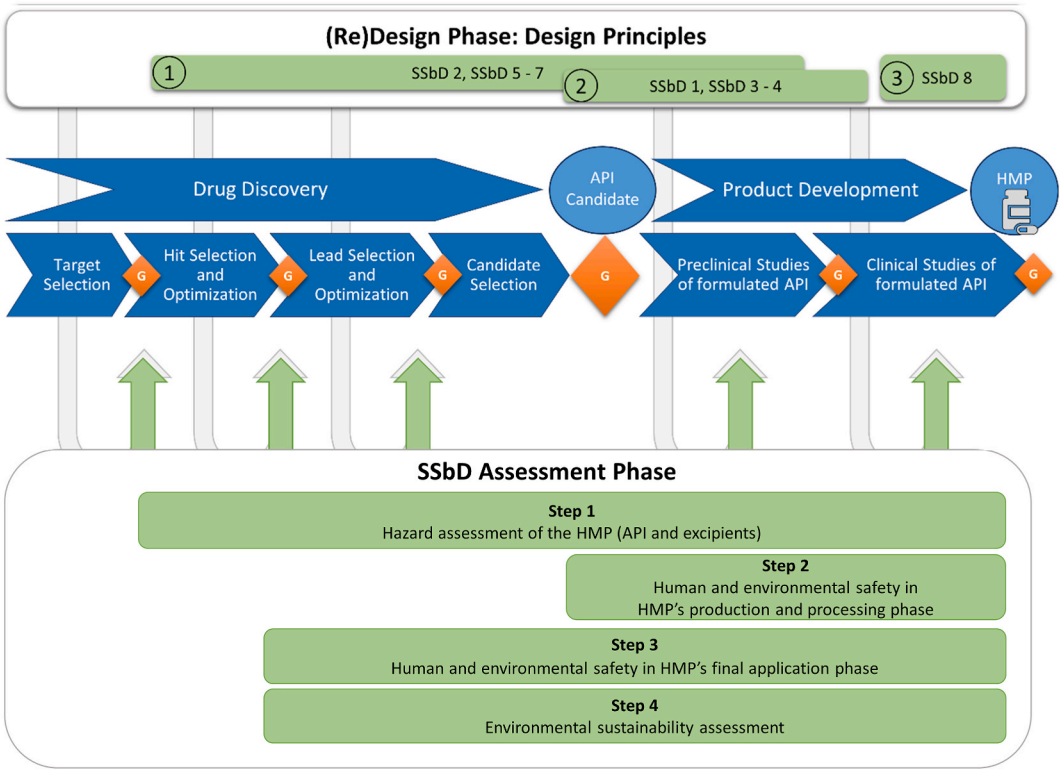

Fig. 3. JRC's SSbD principles (SSbD 1–8) and assessment (Steps 1–4), both integrated in R&D of Human Medicinal Products (HMPs). R&D phases (blue) were added to the generic scheme from the JRC and design principles (upper green part, more details in Section 4.2.1) and assessment steps allocated (lower green part, more details in Section 4.2.2). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Allocation of the SSbD principles to the R&D stages. Grouping of R&D stages by numbering 1–3: 1) drug discovery (dealing with design of molecules/selection of API candidates) and early product development (dealing with scaling-up of the API synthesis regarding all raw materials needed, formulation/excipients), 2) product development (dealing with the research on production processes), or 3) late product development. The numbering of the SSbD principles is also shown in the upper part of Fig. 3.

SSbD principle	Properties of the HMP or its processing	R&D stages
1 - Material efficiency	Use of raw materials, generation of waste	2
2 - Minimize the use of hazardous chemicals/materials	Use of hazardous chemicals/materials	1
3 - Design for energy efficiency	Energy in manufacturing, supply chain	2
4 - Use renewable sources	Resources	2
5 - Prevent and avoid hazardous emissions	Hazardous emissions or pollutants	1
6 - Reduce exposure to hazardous substances	Exposure to chemical hazards	1
7 - Design for end-of-life	End-of-life	1
8 - Consider the whole life cycle	Whole life cycle	3

Using the assessment of the current SSbD framework for a comparison between existing pharmaceutical treatments by healthcare professionals would expand the scope of the SSbD framework as it would subsequently go beyond the innovation phase (Fig. 4). We call this approach *Safe and Sustainable by Comparison* (SSbC). SSbC does not consider the substitution of a chemical (e.g., API) of interest with another one, only, but also by a completely different technology, treatment or behavior, because the substitution occurs at the functionality level, following the concept of functional substitution (Tickner et al., 2015). Comparing medical *versus* non-medical treatments supports strategies like *Rational Use* or *Realistic Medicine* (Alejandre et al., 2022; Eriksen et al., 2017).

As the description of the assessment steps in the SSbD framework is already quite mature the assessment may be easily used outside of the innovation process. The question is whether the assessment methodology in the SSbD framework is adequate to design an assessment system that healthcare professionals can use to make choices for a safer and more sustainable option. Stakeholders have voiced the need for a wide variety of criteria to be part of such a system, addressing dimensions from worker's conditions at production locations, material use, carbon footprint, land use, waste management, to ecotoxicological effects of the API after use by the patient (Heni et al., 2023), which are all criteria that are also part of the current SSbD approach.

Table 3
Allocation of the four assessment steps of the SSbD framework to the pharmaceutical R&D phases. PBT = Persistent, Bioaccumulative and Toxic; M in PMT = Mobile.

Assessment step	Type of input data	SSbD assessment endpoint		Relevant R&D phase (at earliest)
		covered by current R&D	new to R&D	
1) Hazards of API and excipient	Compound's structure (virtual for prediction, material for *in vitro*)	Hazards for patient, e.g., carcinogenicity, mutagenicity	Hazards to environment, e.g., endocrine disruption, PBT/PMT	Hit to candidate selection (API); Product development (excipients)
2) Human and environmental safety during production/ processing	Data on effects and exposure during production/processing	Reaction and solvent guides for synthesis route selection are first approaches	Occupational risks during production and processing (partly new)	Synthesis route selection and upscaling (reg. exposure)
3) Human and environmental safety during use	Data on effects and exposure during use and after excretion	Patient safety; Current environmental risk assessment is performed late in current R&D	Human population through the environment (food chain, antimicrobial resistance)	When dose is being defined (during product development) to define exposure
4) Environmental sustainability	Data on materials, energy consumption, waste, emissions, etc. along the life cycle	Not covered	From simplified to full LCA, following the increasing availability of data and innovation (Abbate et al., 2024)	Simplified LCA as early as possible. Full LCA later because required data collected beyond R&D

Table 4
Annotation of the applicability of the assessment steps from the SSbD framework in R&D of HMPs. PBT = Persistent, Bioaccumulative and Toxic; vPvB = very Persistent and very Bioaccumulative; M in PMT and vPvM = Mobile.

1	Hazard assessment of the HMP (API and excipients)
	Because intrinsic properties are independent of exposure, this Step would already be possible at the hit selection phase, through candidate selection, and later during product development related to excipients. A red-flag system could be implemented in compound libraries to flag compounds of concern, for example based on similarity to other known compounds (read-across). Examples are carcinogenic or mutagenic compounds, but also endocrine disrupting compounds (e.g., due to the mode of action of an API) and those meeting screening criteria for PBT, vPvB, PMT or vPvM. These screening criteria could involve lipophilicity (as indicator for bioavailability or mobility) and molecular structures that indicate persistence in the environment. Of special concern is the presence of very stable molecular moieties such as per- or polyfluorinated groups (definition by OECD, 2021). At a later stage, when more data is available, a rational decision on flagged compounds could be made. Note that the pharmaceutically intended effect may also result in an intrinsic hazard. Thus, in some cases an intrinsic hazard is unavoidable.
2	**Human and environmental safety in HMP's production and processing phase**
	This Step can be undertaken as soon as the final product and its production process are under development (synthesis route development for the API, choice of excipients, final product formulation; typically in early product development) and first assumptions on occupational exposure become available. This allows for risk assessment and mitigation to ensure occupational safety at the production site. Similarly, an environmental exposure assessment should be included by considering emissions to air, soil and water during the manufacturing and processing of the HMP. To this end, a suitable industrial installation would need to be defined, being aware that there are country and manufacturer specifics.
3	**Human and environmental safety in HMP's final application phase**
	Risks to the end users (patients) and the environment after use (*via* patients' excreta) are already assessed within the marketing authorization process. Both should be part of SSbD, since a reduced risk to the environment may have consequences for patient safety as many compound characteristics are interrelated (Vidaurre et al., 2024). An early rough environmental risk characterization, using data on hazards predicted in Step 1 and estimated environmental emissions, may steer further SSbD considerations. For example, if high exposure is unavoidable, it becomes more important to reduce the (eco)toxicity. To be able to do an early risk characterization, data on the intended use is needed, with dosage considerations which may already be made at the beginning of a project and refined along the R&D process. Risks to the environment may be expected to be low (in case of a small patient population) or higher (large patient population and frequent medication, leading to higher exposure to the environment). This rough risk characterization can be refined as the amount of information increases.
4	**Environmental sustainability assessment**
	A full LCA requires a large amount of data to build the life cycle inventory related to the entire pharmaceutical life cycle, which is mostly unavailable at early stages of the R&D process, for instance, for the API building blocks. Whereas obtaining data on the production process of HMPs may be relatively uncomplicated during R&D, availability of data becomes highly complex once production and distribution processes are scaled up and/or outsourced (e.g., because of more complex supply chains that lack data transparency). However, there are simplified methods such as the Fast Life Cycle Assessment of Synthetic Chemistry (FLASC) tool to quantify the environmental performance of manufacturing processes of HMPs (Curzons et al., 2007). This is a trademarked tool by GlaxoSmithKline with confidential underlying data. The model and data analysis are not transparent. Hence, establishment and incorporation of background data to the life cycle inventory cannot be verified (Calvo-Serrano et al., 2018; Güneş and Şengül, 2022).
5	**Socio-economic sustainability assessment**
	This step is not in scope of this paper.

A decision support system is needed to weigh safety and sustainability aspects as options that are safer may not be more sustainable. The relative importance of these aspects may be context- and stakeholder-dependent: for some stakeholders, criteria for environmental sustainability (e.g., carbon footprints, waste or material use) may be considered more important, while others prioritize environmental safety aspects or conditions at production locations. In any case, a decision support system based on the assessment of SSbD may help to prevent burden shifting and regrettable substitutions by considering all aspects, and to come to a more holistic approach.

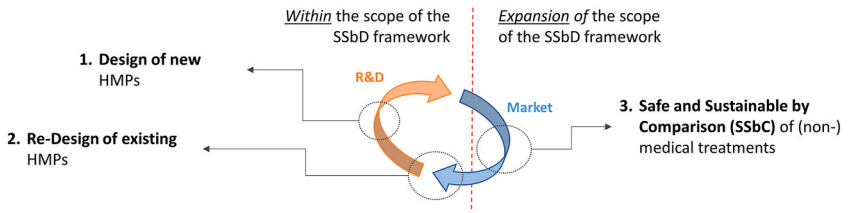

Fig. 4. Application and expansion of the scope of the SSbD framework's assessment. The scope is expanded when assessing existing medical treatments, like HMPs on the market, but also non-medical treatments. As such it is independent of innovation.

The decision support system would need to take into account the dynamic nature of production processes as well as health care systems, where the best choice may also change when physician's guidelines change. Moreover, a product with a high impact should only be replaced by a substance with a low impact if this impact is better per patient dose, and not overall (e.g., if product A has a higher risk to the aquatic ecosystem than product B, based on actual measurements in water, replacing product A by product B may not be a solution if the risk per dose for product B would be higher). A suitable SSbC decision support system will enable a systematic comparison between chemicals (e.g., APIs), products, or treatments, that are already on the market, aiming to correctly choose the safer and most sustainable one.

SSbC may not immediately lead to improvements per product, but is a first step towards increasing awareness for sustainability aspects and to urge companies to provide data on their products. In comparison to applying existing methods like LCA for environmental sustainability, the assessment methodology has the advantage that a holistic assessment of safety and sustainability can be carried out stepwise depending on the data availability. It is a comprehensive framework that combines existing safety and sustainability assessment methods. If enough data is available, less complex assessment steps (e.g., Step 1) can be skipped to carry out a full safety and sustainability assessment directly. If data is limited, these less data hungry steps (e.g., Step 1) could be performed to get a first idea on safety. Another advantage is that SSbD's way of reasoning assists to come to absolute assessments of safety and sustainability. A focus on relative assessment with LCA alone is not sufficient to evaluate the crossing of environmental, social and ecological boundaries. Absolute assessment supports monitoring and evaluating proximity to policy goals.

6. Implications for the applicability of the SSbD framework

6.1. Practical and technical feasibility

This study explored the applicability of the JRC's SSbD framework to the current pharmaceutical R&D process. Conceptually, the SSbD framework can be applied in a straightforward way to (re)design and assess HMPs, with some adjustment (**Section 4**). Compared to other product groups, there is the advantage that much data on safety is already produced in the product development stage. However, there are still large data gaps (e.g., for life cycle inventory and characterization factors for LCA) as well as perception and weighing issues, especially for environmental sustainability aspects, which hampers the practical implementation.

There are many similarities between the SSbD framework and the pharmaceutical R&D process: Both have stage-gate innovation processes and iterative cycles. The SSbD framework is flexible enough to consider sector-specific properties, including those of the pharmaceutical R&D. To operationalize the SSbD concept (**Fig. 3**), data on safety and sustainability need to be generated during the (re)design phase. This is currently a large hurdle to practically apply the SSbD concept during this phase, as these data are not available at that stage yet. It needs further specification which assessment endpoints and criteria for safety and sustainability could be considered, as well as which tools/methods to gather or generate these data. A tiered approach using, for instance, high throughput screens, *in silico* prediction, grouping, read across, and other non-animal approaches is proposed by the JRC for safety testing. Such a tiered approach, starting with *in silico* predictions and efficient *in vitro* screens that allow a high throughput, would also be useful for environmental safety testing within pharmaceutical R&D. However, not all of the *in silico* tools proposed by the JRC that are working for bulk chemicals of interest for pharmaceutical products (e.g., solvents, excipients and disinfectants) will work for structurally more complex, bioactive and often ionizing APIs. Thus, there is an urgent need for suitable *in silico* tools and high-throughput methods to assess possible environmental risks, especially for early phases of R&D where thousands of compounds need to be tested. Currently, research projects, funded (partly) by the EU, like PREMIER[2] , are working on the development of such tools. Besides this, tools and data are needed for sustainability assessment. In research projects such as TransPharm[3] and PARC[4] but also industry initiatives such as the Pharmaceutical Supply Chain Initiative, experts are working on this from different angles. Preferably, these systems should be harmonized and eventually become part of regulatory procedures. Guidance is required to properly identify and use the relevant tools of the toolbox for a specific context.

Regarding the redesign, there is the advantage of using existing data. Most of the APIs with a known risk are generic molecules and

[2] PREMIER: Innovative Medicines Initiative 2 Joint Undertaking, grant agreement No 875508.
[3] TransPharm: Horizon Europe grant agreement No 101057816.
[4] PARC: Horizon Europe grant agreement No 101057014.

it may be very difficult to replace them on the market, earn back development costs, and convince doctors and patients to replace their current medication. All new ((re)designed) APIs need to undergo all regulatory safety testing steps, but also APIs that are produced using a new synthesis process often need a new drug master file including many tests (EMA, 2018). Showing bio-equivalence requires a lot of time and resources, whereas it is also a challenging and multi-stakeholder process to adapt regulation to address this. However, new compounds can be patented, which is the basis of new business opportunities.

6.2. Harmonization of methodology, criteria and data on SSbD

Next to practical and technical feasibility, additional scientific challenges need to be addressed to further promote the implementation of SSbD into pharmaceutical R&D. First, in contrast to the SSbD definition in the CSS, the sustainability definition in the SSbD framework lacks a reference to the amount of chemical/material used or produced. Since 'sustainable', like 'safe', is not an intrinsic property, considering amounts of substances used and emitted into the environment and their resulting environmental concentrations is crucial, especially for sustainability evaluation in relation to planetary boundaries (Rockström et al., 2009). In this direction, new research fields have explored the concept of absolute sustainability (Li et al., 2021).

Regarding safety, Steps 1 and 3 of the SSbD framework are partially already considered in common pharmaceutical R&D, while Step 2 is not part of common R&D. The authorization process in the EU currently considers environmental safety after the use stage (*via* excreta), only, and has limited to no consequences for HMP's authorization and use. Furthermore, the necessary information is currently only available for part of the APIs, as this information has only been generated for active ingredients in HMPs authorized after 2006. One of the issues that needs to be explored is whether and how cut-off criteria for hazards (Step 1) are applicable to pharmaceutical R&D. During early stages of R&D, it may be more suitable to use red flags, indicating problematic molecules or structural features, so that they can either be discarded or improved at later R&D stages. Red flags may become more important when applying SSbD to an HMP intended for a significant patient population. However, if hazard prevention is not feasible during innovation, for instance, if hazard is based on the intended therapeutic effect (such as for hormones or anti-neoplastics) and there is no alternative, the SSbD approach could turn into a risk-based approach. This approach could then aim to mitigate risks, by, for example, reducing exposure through the improvement of the drug delivery method.

Regarding assessment Steps 2 and 3, this study proposes to consider consumers' exposure to HMPs together with the different end-of-life scenarios in Step 3, independently of potential occupational exposure (explained in **Section 4.2**). In the context of end-of-life scenarios, environmental exposure is mostly covered by excretion of the pharmaceutical which overlaps with the end-of-life meaning (de Soete et al., 2014). Workers' exposure during waste/wastewater treatment of the HMP can be considered negligible compared to the impact on the environment (e.g., Michael et al., 2013). In addition, the proposed structure adds the inclusion of the environmental safety assessment both in the case of the presence and absence of a WWTP as both scenarios are possible (UN Water, 2017).

Step 4 of the framework, addressing environmental sustainability aspects, is not part of common R&D. Thus, additional effort is needed to characterize all steps of the SSbD framework so that all aspects can be considered so the decisions made reflect safety as well as sustainability. Most HMPs are not covered in life cycle inventories, which makes impact characterization of Step 4 for HMPs and their ingredients very difficult. Existing impact categories mapped in LCA may not be ideal for HMPs. For instance, assessment methods do not cover antimicrobial resistance, endocrine disruption or other risks due to subtle ecotoxicity, but could be addressed (Nyberg et al., 2021).

SSbD aspects should be weighed and assessed holistically (van Wilder et al., 2024). SSbD aspects need to be weighed carefully against each other, treatment benefits, and other factors like costs. This overall weighing is needed to prevent (otherwise unknown) trade-offs, which could lead to regrettable substitutions. One reason is that improvements in one aspect (e.g., safety related) may lead to negative consequences in another aspect (e.g., sustainability related or within sustainability). Positive aspects should always outweigh any negative aspects. The fact that HMPs are intended to fulfil a medical need requires a special, more patient-centered assessment strategy. Including environmental safety and sustainability concepts into this decision may not be easy. Thus, the way forward should be to (re)design (SSbD) or choose (SSbC) HMPs that fulfil additional safety and sustainability criteria where possible, without compromising access to medicines and well-being of patients. This is reflected in the first G of the GREENER concept, standing for "Good practice for patients" (Moermond et al., 2022). HMPs, expected or known to cause environmental impacts, could be prioritized for (re)design (of their APIs, delivery methods, production methods, etc.). This needs a regulatory push, and the creation of business opportunities, by procurement criteria for instance that take safety and sustainability aspects into account.

6.3. Drivers for the SSbC implementation

Although the SSbD framework was setup for innovation purposes, it is also conceptually and practically useful for comparison purposes of existing pharmaceutical treatments, i.e., beyond the innovation process (SSbC, Section 5). The driver for SSbC goes beyond the drivers for the pharmaceutical industry to become safer and more sustainable (as identified elsewhere, Puhlmann et al., 2024). SSbC would be part of the whole life cycle of an HMP, where stakeholders may desire to make safer and more sustainable choices. This could be for procurement, reimbursement policies, professional guidelines, prescription and use of HMPs. Before being able to operationalize any SSbC assessment framework, decision-makers in the healthcare sector should be aware of environmental issues related to pharmaceuticals and should understand the various aspects that are part of SSbC. Therefore, education and training are key. A societal push may also motivate decision-makers to deal with concepts like SSbC. Awareness can lead to initiatives by stakeholders in healthcare, as best practices on green and sustainable pharmacy in Europe show (PGEU, 2019).

In line with policy and societal ambitions, the SSbC is a first step to urge companies to provide data and also to improve their HMPs

to become significantly safer and more sustainable. To be able to implement SSbC along the life cycle of HMPs, this should be part of a holistic assessment system. This would not only include safety and sustainability, but also conventional health technology assessment aspects like efficacy and cost-effectiveness, leading to a footprint (negative aspects) as well as a handprint (positive aspects) of treatment (van Wilder et al., 2024).

Although SSbC would be applicable to existing HMPs, and more data may be available, the actual use of an assessment system for the safety and sustainability of HMPs, even when they are already on the market, is currently still hampered by a lack of (harmonized) methodology and a lack of data, especially regarding their sustainability. The level of detail required for the data and its reliability needs to be discussed towards the ability to distinguish between treatments, which is a challenge especially for environmental footprints of individual products. The lack of insight into distribution processes and the fact that distribution lines constantly change make it highly challenging to assign a metric for a carbon footprint to an individual product.

To be able to operationalize SSbC, methodology and data requests need to be internationally harmonized, preferably also in a regulatory framework. Related guidance documents could also support harmonization. Pharmaceutical companies should report environmental impact data transparently in their product information (Piët et al., 2024). Sustainability experts of procurement agencies or independent parties (e.g., collaborating authorities) should be enabled to make SSbC assessments based on the provided data. For procurement, a number of initiatives currently test the inclusion of criteria to reduce environmental impact (NHS, 2024; Norwegian Hospital Procurement Trust, 2022–2023; Ruiz, 2022). The results of the SSbC assessment should be part of a system that is easy to understand and/or use by healthcare professionals (e.g., doctors, pharmacists).

7. Recommendations and outlook

This paper showed that the SSbD framework is conceptually applicable to pharmaceutical R&D. Hence, the SSbD framework by the JRC can guide the (re)design of safer and more sustainable HMPs. If the pharmaceutical sector wants to apply the SSbD framework during R&D, it is recommended to strengthen the assessment of environmental risks of APIs, for example, by considering drivers for environmental risks (like persistence, ecotoxicity and environmental input) during hit and lead optimization. The impacts of excipients of the pharmaceutical product need to be assessed as well. Quite new to R&D, but required for SSbD, would be the consideration of environmental sustainability aspects along the entire life cycle of HMPs. On top of that, the assessment from the SSbD framework can be used independently of the innovation process to compare different types of (non-)medical treatments, for example to prescribe a safer and more sustainable treatment. This decision-making, i.e., *Safe and Sustainable by Comparison*, is needed for a more prudent use of HMPs.

We identified urgent research needs on.

- suitable *in silico* tools and high-throughput *in vitro* methods on environmental safety and sustainability, applicable in early phases of R&D. Especially the assessment of APIs requires special tools and methods as they are bioactive by definition and structurally more complex than common chemicals.
- meaningful, pragmatic and clearly defined assessment criteria to specify the generic description in the SSbD framework for HMPs. This includes characterization factors for LCA. LCA of HMPs should also cover antimicrobial resistance, endocrine disruption and subtle ecotoxicity. When refining the hazard criteria, it needs to be considered that APIs can cause (eco)toxicity, such as endocrine disruption, due to their mode of action. In this context of pharmacologically required properties, pros and cons of applying cut-off criteria for the most harmful substances (e.g., endocrine disruption cat. 1, PBT/vPvB, PMT/vPvM) need to be discussed.
- a holistic assessment system on safety and sustainability including a weighing system of different parameters, that follows key safety and sustainability issues and considers different purposes (e.g., during the innovation phase *versus* by different healthcare actors). This system should support the decision-makers in HMP development and facilitate comparison between HMP(s) and/or (non-)medical treatments. Including the social dimension of sustainability would also take the degree of medical need into account.

To advance in SSbD, the pharmaceutical sector provides an excellent area to develop such criteria and tools which could then also be applied to other sectors.

CRediT authorship contribution statement

Neele Puhlmann: Writing – review & editing, Writing – original draft, Conceptualization. **Elisabetta Abbate:** Writing – review & editing, Writing – original draft. **Klaus Kümmerer:** Writing – review & editing. **Agnes G. Oomen:** Writing – review & editing. **Ad M.J. Ragas:** Writing – review & editing. **Caroline Moermond:** Writing – review & editing, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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