Eco-design and medicine: Opportunities to implement eco-design in the pharmaceutical R&D process

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A B S T R A C T

The pharmaceutical sector has the societal duty to make medical healthcare products both available and affordable. But like any human activity, it is not neutral in terms of environmental impact. Therefore, and like any industry, the pharmaceutical sector needs to consider the environmental aspects into its product design and activities in order to reach a sustainable production and consumption patterns, as defined by the Sustainable Development Goal (SDG) 12 of the United Nations. With a holistic perspective, the eco-design concept is an approach that aims to integrate environmental aspects into product design. To contribute to the SDGs, the pharmaceutical industry needs to consider the environmental impacts of its products. Usually, experts within Research & Development (R&D) do not have the proper level of knowledge to integrate the environmental aspects, in a Lifecycle perspective, into their decision making. Even so, those parameters are not yet part of the New Product Development (NPD) process of the medicine product. With those elements in mind, the aim of this paper is to understand which phases of the pharmaceutical R&D process represent an opportunity to eco-design such products.

We proposed two qualitative experimentations with, first interviewing ten practitioners of R&D; and second, with an assessment of the medicine NPD process and related deliverables, based on LCA results. The use of such results to investigate potential key contributors during NPD stages does not seem to be explored yet, especially for the pharmaceutical sector.

Results show that eco-design approaches can be performed all along the development of a pharmaceutical product. Main eco-design levers appear in parallel to the clinical phases 2a and 2b, in other words, when the tests on the final marketed form are initiated.

1. Introduction

As a marker of the integration of the sustainability by the international community, the United Nations has set 17 Sustainable development Goals (SDG) (2020). From a pharmaceutical sector point of view, the SDG three called "Good health and well-being" is intrinsically part of its societal duty. If we take a closer look on environment, like each industry, the pharmaceutical sector is a contributor to reach a responsible consumption and production patterns, as defined by SDG 12. And like any human activity, this sector is a contributor to the goals 13; 14; 15, respectively climate action; life below water; life on land. By integrating the environmental aspects into product design, eco-design is an approach which can support industries to contribute to these SDGs and reach the resilience of their activity.

From a scientific point of view, the planetary boundaries are setting a framework of "nine processes that regulate the stability and resilience of

Abbreviations: ACS, American Chemical Society; API, Active Pharmaceutical Ingredient; ICH, International Council for Harmonization; LCA, Life Cycle Assessment; LCM, Lifecycle Management; NDA, New Drug Application; NE, Novel Entities; NPD, New Product DevelopmenT; PEF, Product Environmental Footprint; R&D, Research & Development; SDG, Sustainable Development Goals.

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the earth system" (Rockström et al., 2009). A recent update proposed a quantification of the Novel Entities (NE) boundary (Persson et al., 2022). Medicine products are made with compounds with an activity for humans or animals, called Active Pharmaceutical Ingredient (API). And, as product with a potential release & toxicity for the environment (Taylor and Senac, 2014), can be consider as NE. Some trace of consideration pollution for the environment from medicine can be found around 1970 (Hignite and Azarnoff, 1977) and are nowadays raised as a major concern (Wilkinson et al., 2022). In eco-design, those elements are only a part of the environmental impact. For instance, with the COVID-19 vaccines, Klemeš et al. are integrating in their environmental assessment not only the energy consumption of the production of the products, but also the one related to all activities (e.g.: energy of vaccination center, disinfectant used) required to administrate the doses to the patients (Klemeš et al., 2021). The point is to integrate a Lifecycle mindset into the NPD process of medicine side by side with the holistic view of the environmental impacts of the product and related activities. This mindset seems not to be widely spread in this sector and the New Product Development (NPD) of medicine products should embrace this eco-design journey.

In order to reach a systemic approach of eco-design, companies should work on three levels; the macro, by defining a clear strategy; the meso, by integrating environmental requirements into NPD; and the micro, by supporting teams with operational tools (Brones and Monteiro de Carvalho, 2015). The tools will most likely depend on the key users identified at the meso level. The macro level is a strategic decision, intrinsic of each company at a global level. As eco-design is not fully embedded within the pharmaceutical sector, the research question below, related to the meso level, appears.

RQ: In which steps of the pharmaceutical R&D process is there sufficient information available to support eco-design activities?

To answer this question, we performed two experimentations in order to feed the two hypotheses below.

H1. Eco-design activities can be focused on specific steps of the medicine NPD

H2. Quantitative environmental assessment, such as Life Cycle Assessment, can support decision making during the pharmaceutical NPD

To address this problematic, we proposed some theories around New Product Development, pharmaceutical development, and eco-design. The purpose was not to have exhaustive literature reviews, but to set the overall context of this research with these related fields. After explaining the methods of the two experimentations performed, results of the experiments are then exposed to engage discussion about main limits and interpretation are suggested. Finally, a conclusion of the work with perspectives of research is presented.

2. Theory

The purpose of this part is not to propose an exhaustive literature review on pharmaceutical R&D processes. We aimed to illustrate its main characteristics through an integrative review as defined by Snyder (2019).

We also proposed a quick overview of eco-design practices. Like previously, the point is not to have a full literature review of this research field. We aimed to set a bit of context of the two experiments, to finally highlight how they fit in a broader eco-design research framework.

2.1. Pharmaceutical R&D/NPD

The International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH) described the pharmaceutical lifecycle of a medicine through four steps (Fig. 1), the pharmaceutical development, the technology transfer, the commercial manufacturing, and the product discontinuation (ICH, 2008).

Even if Ramnarine et al. (2017) described the process as linear, usually, the technology transfer is included within the pharmaceutical development. The beginning of this phase starts when the medicine shows positive results (efficacy and safety for patients) in the early development phase. The technology transfer can start somewhere between the clinical phases 2a and 2b, as shown in Fig. 2, to optimize the time. During commercial manufacturing, the production of a medicine can be transferred from one site to another. A process of technology transfer is then initiated.

As we aimed to set a framework of eco-designers within the NPD of medicine product, we focused the rest of the paper on the sub-steps of the pharmaceutical development which can be identified within four parts: research, early development, late development, and market as shown in Fig. 2.

The purpose of target identification is to understand the origin of a disease and the potential targets for intervention. In terms of product development, it allows the project team to have a better vision of potential markets and related therapeutically products. During the lead discovery, researchers aim to screen and filter molecules with a therapeutical interest.

The Active Pharmaceutical Ingredients (API) are investigated in preclinical trials to evaluate preliminary effects. The preclinical trials are performed in the laboratory with cells (in vitro), animals (in vivo), and through informatic models (in silico). In terms of design, teams are asked here to provide products quickly. The challenge in this step is to make as much API as needed for all necessary tests.

In clinical phase 1 the first tests in humans are performed. The objective is to identify the kinetic profile of the API and to assess the metabolism. In other words, researchers are looking for the way on how the API is reacting and what are the metabolites, resulting of the reaction. The panel is constituted of healthy probands. Regarding the design of the medicine product, a first galenic form of the drug product is set but will usually not be the same as the final approved product.

If results are relevant, the phase 2a is initiated. The purpose is to determine the therapeutic dose which will have efficacy and minimal side effects. Generally, the galenic form of the product tested is similar to the final approved product. Indeed, the tests must reflect the effect of the final product who will be available to the patient to identify and prevent potential side effects.

The goal of phase 2b is the same as of phase 2a but with a larger panel of patients. The efficacy of the new medicine is then determined during phase 3.

When all stages are performed and have yielded good results, an application for authorization is sent to the authority related to the country targeted for the market. Each country has specific regulations, and the documentation must be adapted to fulfil country requirements.

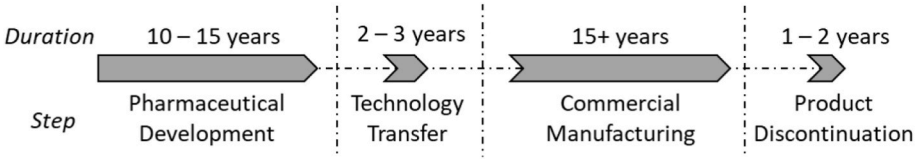

Fig. 1. Ramnarine Lifecycle steps of medicine (Ramnarine et al., 2017), based on ICH guideline.

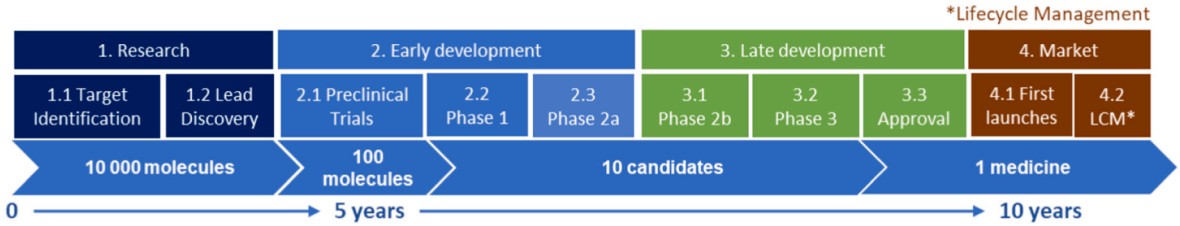

Fig. 2. Sub-steps of the Pharmaceutical Development of medicines to the LCM.

After the first launch, the life of the product continues, often referred to as phase 4. In phase 4, after market authorization, the new medicine is still tracked but in real conditions to ensure safety of patients and discovery and documentation of rare effects.

These steps explain the specific timeframe of the pharmaceutical NPD. This process is necessary to ensure patient safety from the R&D activities to the availability of the medicine product.

It is important to notice that the Lifecycle Management (LCM) within the pharmaceutical sector differs from the generic one. In this sector, LCM can be defined as *"Optimizing lifetime performance of pharmaceutical prescription brands, every time, within the context of the company's overall business, product, and project portfolio."* (Ellery, 2012). Therefore, it starts after the first launches of products, also defined as "commercial manufacturing" by the ICH (as shown in Fig. 1). This paper does not cover this stage or the product discontinuation one. For the rest of the paper, the terms "pharmaceutical development" and "pharmaceutical NPD" are considered as synonyms. They include all the sub-steps described in Fig. 2 except the LCM.

Regarding the academia perspective of the pharmaceutical R&D process, it is possible to identify five main research topics of interest to practitioners: research productivity, technology transfer, process management, clinical development, and healthcare marketing (Romasanta et al., 2020). None of these areas include environmental aspects or similar expression in their key words, showing a lack of integration of such aspects.

We can also mention Emara, who performed a review of Life Cycle Assessment of this sector, available in the literature. Less than 30 have been published in peer-reviewed journals, mainly with a cradle-to-gate scope (Emara et al., 2018).

When we are talking about eco-design within the pharmaceutical sector, it seems unfair to not talk about the Green Chemistry. The ACS Green Chemistry Institute described the first main milestone of this philosophy in 1962, with the scientific book "Silent Spring" of Rachel Carson (American Chemical Society, 2021). The Pollution Prevention Act of 1990 in the US had a key role in the development of this concept (Anastas and Williamson, 1996). The definition of this field has evolved through the decades, but the community seems nowadays to agree on 12 principles who set the approach (Anastas and Eghbali, 2010). As part of small molecules-based medicines, the chemistry within the pharmaceutical sector does not make an exception. Literature shows that companies such as Pfizer (Tucker, 2006) (Alfonsi et al., 2008), GSK (Alder et al., 2016), Bristol-Myers Squibb, AstraZeneca, Takeda, Novartis (Borovika et al., 2019), Sanofi (Prat et al., 2014) and others have integrated these principles in their activities. For instance, as described by Ang, Circular economy seems to have a momentum in the pharmaceutical sector since the publication of a white paper in 2016 by the European Federation of Pharmaceutical Industries and Association (Ang et al., 2021). But those publications are mainly turned in alternative chemistry and few of them consider processes. Moreover, the chemistry represents only the small molecule piece of the broader picture of the pharmaceutical sector as described by the ICH (2012). The holistic approach proposed by the eco-design seems therefore relevant to implement within this industry.

2.2. Eco-design approaches

The eco-design concept is defined as a *"systematic approach that considers environmental aspects in design and development with the aim to reduce adverse environmental impacts throughout the Lifecycle of a product"* (ISO, 2020). It is possible to find designers with an environmentally responsible approach earlier in the 1960's (Dewberry, 1996). Nevertheless, the crystallization of this field of research appeared in the 1990's within the scientific community (Boks, 2006).

Schäfer provided a segmentation of this discipline into five main areas of research: terminology, evolution, barriers & success factors, methods & tools, and synergies with other research disciplines (2021). Brones et al. identified around 52 integration models of eco-design and studied them to propose a unique framework (2015) as shown in Fig. 3. The authors described this model with a vertical and a transversal integration. The first one is divided within three levels: macro for the strategic part (e.g.: strategy & corporate objectives), meso for the tactical (e.g.: integration of environmental requirement into product design) and micro for the tools (e.g.: environmental assessment tools). The transversal integration, also called "soft side", is around the culture of a company and the human factors.

Literature abounds of eco-design tools frameworks (Bovea and Pérez-Belis, 2012; Jugend et al., 2020; Rossi et al., 2016; Rousseaux et al., 2017; Vallet et al., 2013; Varžinskas et al., 2020). Non exhaustively, we can mention product related (Kozderka, 2016; McAloone and Pigosso, 2018; Rio et al., 2010), managerial (Gouvinhas et al., 2016; Paula Pinheiro et al., 2018; Pigosso et al., 2013) or communication one (Del Borghi, 2013; ISO, 2017a, 2017b, 2006). This diversity of tools offers a large range of options to designers, who should be able to integrate environmental aspects into NPD requirements.

2.3. Summary of the theoretical background

The pharmaceutical NPD is well known due to common regulations. It is mainly explained by the necessity to ensure both effectiveness of the product and safety for the patient. The field of eco-design research can be set somewhere around the 1990's. The literature proposes tools to integrate this approach within industries.

Despite that, the pharmaceutical industry does not have integrated the environmental impacts of products, into their NPD process in a holistic way. It can be noted that, within the pharmaceutical R&D, neither the field of process management (Romasanta et al., 2020) nor the environmental aspects of products are topics well addressed to the experts of this sector. Therefore, a first step to understand where eco-design approaches could fit into medicine NPD is proposed in this paper.

3. Methods

This research includes two experimentations. The first one was based on semi-structured interviews of R&D practitioners, involved during the product development. The second experimentation was built with a qualitative assessment method.

The two approaches have pros & cons (see Table 1). Main ones are summarized in the table below, based on literature for the semi-

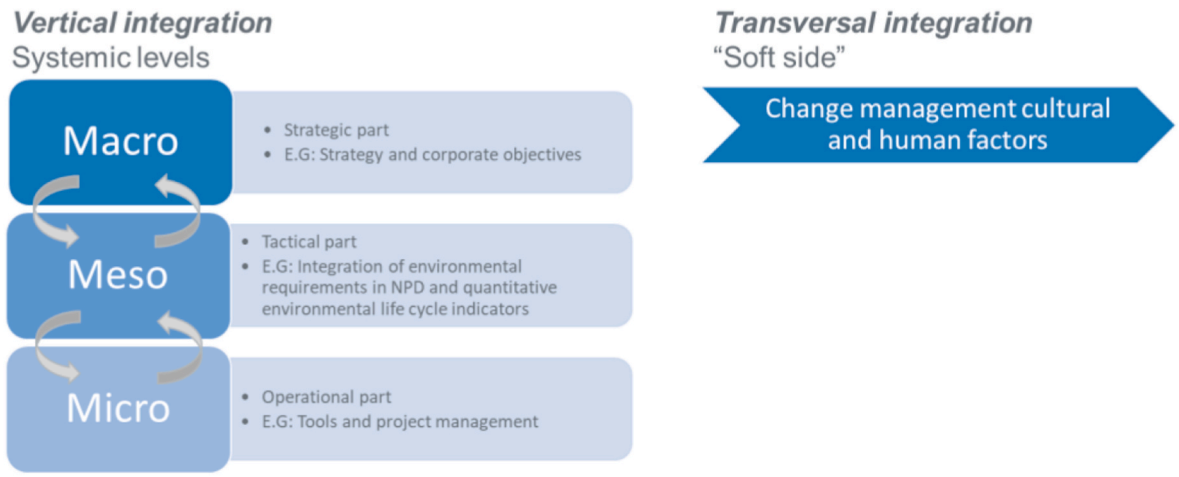

Fig. 3. Brones eco-design integration model: combining vertical and transversal integration.

Table 1
Main pros & cons of the semi-structured interview and the qualitative assessment method approaches.

Approach	Pro	Con
Semi-structured interview (Doody and Noonan, 2013; Kallio et al., 2016)	• Versatile & flexible • Reciprocity between interviewer & participant • Space for participants' individual verbal expressions • Interviewee can ask for clarification Enable complex questions	• Basic knowledge required • Time consuming *(e.g.: preparation, conduction, transcription, analysis)* • Language barriers Potential bias *(e.g.: nonverbal expression can influence interviewee)*
Qualitative assessment method	• Evaluation and results are based on objective methods • Results are rationalized Easy to use	• Values are based on knowledge and subjective perspective of expert involved Potential inflation of score with a conservative approach

Table 2
Main characteristic summary of the interviewees.

Participant	Position, Expertise	Related years of expertise	Country	Environmental knowledge	Con
P1	R&D, Environment, Health, Safety	14	United States	Regulatory based	
P2	R&D, Chemistry	24	France	Green Chemistry	
P3	R&D, Biotechnology	14	France	No	
P4	R&D, Biotechnology	12	France	No	
P5	R&D, Outsourcing	30	France	No	
P6	R&D, Medical devices	19	Germany	Contributed to a LCA study	
P7	Industrial, Packaging	25	France	Contributed to a LCA study	
P8	R&D, Vaccines	35	Canada	No	
P9	Market insights, Over the Counter	7	France	No	
P10	Procurement, Medical devices	20	France	No	

structured interview, and on our perception for the assessment method.

The semi-structured interviews rely mainly on both knowledge and understanding of the topic of interviewer and interviewees. Results should be taken carefully due to these potential biases.

These results were balanced by assessing the potential environmental impacts of the deliverables from the R&D process. This second study was launched in parallel to confront the results to the ones of the semi-structured interviews. In that sense, it represents a complementary approach to be able to confirm the convergence point.

3.1. Practitioners' interviews

The first experiment consisted of semi-structured interviews with ten practitioners of the one multinational pharmaceutical company. The purpose was to identify through them the main steps of the medicine NPD who could feed an eco-design approach. Aspect of the expertise of interviewees and environmental knowledge are summarized in Table 2. They were selected due to their pharmaceutical R&D and, or medicine product expertise and to be as much as possible complementary to cover most of process development. 60% of the participants claimed to not have specific knowledge in environment. Topics raised during the interviews are summarized in the appendix 1 and goes from the product portfolio scope, the NPD triggers, competencies for designers, indicators, or environmental data generation.

Data were processed by the eco-design expert involved as the interviewer. Then, a round of review was performed by the eco-design lead of Sanofi and a PhD student, to correct the misinterpretation of the interviewer, which was not an expert of the pharmaceutical industry.

The eco-design lead of Sanofi had a PhD in chemistry, worked for six years in R&D and 15 years at global level in the field of risk prevention. The PhD student had a background of one year in pharmaceutical R&D and four years in this industry as risk prevention engineer.

The interviews were performed between January 12, and January 21, 2021. It lasted 45 min to 1 h and a half, with an average of 1 h.

To avoid biases linked to pharmaceutical knowledge-perception, the interviews were carried out by an independent interviewer who held a PhD in eco-design. He was selected due to his six years expertise in eco-design within several industries in France and the lack of familiarity with pharmaceutical products.

3.2. Environmental aspects root cause within R&D decision making

The second experiment was based on a qualitative evaluation. We

have made available to an environmental expert of Sanofi the results of a Life Cycle Assessment (LCA) of an existing medicine. The expert involved was part of Sanofi for 32 years, with responsibilities around climate risk management and previous experience regarding LCA coordination, environmental reporting & energy, facility management in R&D.

As it is not the purpose of this paper, we will not go into the details of the LCA results. They were used as raw data, to identify the decision steps, during the R&D process, that may have led to the environmental impacts assessed. The main characteristics of the LCA used are summarized in the Table 3.

The list of the deliverables and key design decisions during the R&D process was made available to the same expert. This list was composed of 263 deliverables. We can mention for instance the necessity to identify the main therapeutic use, the New Drug Application (NDA), the stability of the product or the industrialization choices with related technologies.

From these two elements, a first assessment was conducted through the list of all deliverables within the four stages of the pharmaceutical development process (as described in Fig. 2). The purpose of this step was to identify the deliverables with "eco-design potential". We defined it as a deliverable who may have a direct/indirect impact on either the product specifications (e.g.: storage condition), the industrialization (e.g.: supplier selection), the supply chain (e.g.: type of transport), the use & end of life (e.g.: metabolism rate) or other data generation (e.g.: pharmacological profile) useful to assess the environmental profile of the product.

A score of the potential environmental impact of the related deliverable, based on the LCA results and on four indicators of the PEF (global warming, freshwater eutrophication, freshwater ecotoxicity, water scarcity footprint), was then set between one (low) to four (high impact). As each step of the lifecycle may contribute differently to each indicator, this approach was performed to each deliverable, per lifecycle step (the raw materials are included within API; formulation and packaging) for the four indicators. An example of the calculation is provided in appendix 2.

4. Results

Qualitative results are described for both the R&D practitioners' interviews and for the second experiment regarding R&D decision making to then engage a discussion regarding limits, highlights, and convergence points.

4.1. Practitioners' interviews

Three additional macro design steps were identified, discovery, clinical manufacturing, and industrialization. The discovery takes place during the research phase. The clinical manufacturing is between the preclinical trials and phase 3. Finally, the industrialization takes place at the end of the preclinical trials until the LCM and usually includes the technology transfer mentioned in Fig. 1.

Table 3
Main characteristics of the LCAs used for the study.

Characteristic	Description
Year of the LCA	2020
LCA method	Product Environmental Footprint (PEF)
Function	Treat symptoms
Functional Unit	One gram dosage per drug intake for one adult *(equivalent of the dosage of Active Pharmaceutical Ingredient into one tablet)*
Reference flow	One tablet
API	Chemical based
Galenic form	Tablet
Packaging	Blister PVC/Aluminum
System boundary	Cradle-to-Grave *(Raw material; API synthesis; formulation; packaging; distribution; use & end of life)*

During interviews, all participants with no environmental knowledge were at first focused on their own activities and understanding of the potential environmental impacts (e.g.: *"We use a lot of paper, we could reduce our impact with the digitalization"*). Results of the discussions are described below.

- Discovery

During discovery, APIs are synthesized by all means in order to eliminate ones without therapeutical potential. Synthesis routes are therefore at laboratory scale, with a high margin of error in terms of environmental assessment as both attrition rate and uncertainties are high.

Data regarding raw materials are linked to the APIs manufactured at the laboratory scale and does not represent at all the ones for the marketed medicine. The same goes for the energy of processes, the localization of manufacturing, wastes, emissions and transportation.

Choices made during this step will impact indirectly the lifecycle of the product. For instance, monoclonal antibodies are today expected to degrade to small peptides and individual amino acids. In other words, not harmful for the environment, which is not the case for most of small molecules based on usual chemistry. As the level of uncertainty is high at this stage, qualitative eco-design guidance could be interesting to implement.

- Clinical manufacturing

At this step, first production scale up appears to launch trials. It takes place at pilot scale, and specifications of the product are explored. The API, formulation (final form of the product taken by the patient. e.g.: tablet, ointment, liquid injectable), packaging begins to be set as the trials need to be conducted on a form representative of the marketed one.

Estimation of energy required for the processes, waste generation and other emissions can be performed. Transportation starts to be investigated, same as the usage (e.g.: administration route), manufacturing plant, and preliminary eco-toxicity profile. An eco-designer could seize the opportunity of the generation of such data to provide semi-quantitative insights, based on LCA approach, to guide decision making.

- Industrialization

When the API shows positive results, industrialization is launched to manufacture the product with the same pharmacological properties studied during trials.

Accurate data regarding raw materials, energy consumption, localization of manufacturing plant, waste generation and other emissions, transportation, usage and end of life are available or being to be. As data begin to be more accurate, the eco-designer could support the development process by giving quantitative through LCA.

4.2. Environmental aspects root cause within R&D decision making

A first assessment was conducted through the list of all deliverables within the pharmaceutical development process. The purpose of this step was to identify the deliverables with an "eco-design potential" as defined in chapter 3.2. Results are summarized in the Table 4 and showed an average of 36% of deliverables with an "eco-design potential", up to 43% in the research phase.

After this first assessment, a score between one (low environmental impact) and four (high environmental impact) was performed for each deliverable. Data in Fig. 5 represents the breakdown by lifecycle stage of the level of influence of the deliverables and example of calculation is provided in appendix 2. In every step, the early development is the most

Table 4
Number of deliverables and potential eco-design ones per sub steps of the pharmaceutical development.

NPD step	Number of deliverables	Deliverables with eco-design potential	Con
1. Research	49	21 43%	
2. Early development	84	29 35%	
3. Late development	109	21 19%	
4. Market	72	23 32%	
Total	**263**	**94 36%**	

impactful (between 37% and 40%). Less significantly, the late development contributes secondly (between 22% and 28%) to the climate change impact profile. Then, depending on the lifecycle step, research and market are sharing the third and last places (between 15% and 23%).

A similar profile can be observed for the water scarcity footprint. But the ones for freshwater ecotoxicity and freshwater eutrophication differ. Even if for all the indicators, the early development seems to be the major contributor (between 31% and 40%), for both freshwater ecotoxicity and freshwater eutrophication, the research stage contributes in second position to the API, formulation, and use & end of life steps (between 27% and 29%). The late development comes then for these lifecycle steps (around 21%). Still for freshwater ecotoxicity and freshwater eutrophication, the late development seems to come in second place of contributor for packaging and distribution (between 28% and 31%) and the market at the third one (between 19% and 21%). The figures are provided in appendix 3. The Table 5 propose a global view with a breakdown of eco-design potential with an aggregation of the lifecycle steps.

5. Discussion

In this part, we aim to expose the major's highlights, convergence points and main limits.

5.1. Practitioners' interviews

This first study allowed us to see that eco-designers could be set mainly between phase 2a and 2b. Qualitative or quantitative approaches could be performed all along the NPD and should be adapted, to both available data and the environmental levers, within each step.

Despite our effort to have experts knowledgeable of the medicine NPD, two limitations linked to this panel can be mentioned. First, even if the regulation requires some harmonized steps within the pharmaceutical sector, each company may have their own way to integrate these requirements. The experts involved were only part of one multinational company.

Secondly, medicines are complex products. It is therefore always possible to find experts with a targeted activity and related expertise within a sub-step of the pharmaceutical development. Our approach was to interview people with both an overview of the process and operational knowledge. Therefore, the interviews could gain in deepness by adding other complementary expertise within the pharmaceutical NPD.

The data available for an eco-design approach was explored during the interview but due to the complexity of the product, deep levels of granularity were not defined.

5.2. Environmental aspects root cause within R&D decision making

Like the previous approach, the purpose of the experiment was not to catch all the specificities of medicines. Additionally, in terms of development, the deliverables are most likely different due to the different processes and specifications of such products. In this approach, we did not include these kinds of complexities.

In Fig. 6, the profile of the curve seems to tend to a gaussian form. "anomalies" can be noted for the phases 1 and 3. For phase 1, no significant deliverables were identified. For the second one, as the product is still in trials during phase 3, modification of medicine should be still feasible or at least have a higher potential than the approval phase where everything is frozen for the market authorization. A misunderstanding of the steps and related eco-design potential may explain the results here.

One of the limitations of the approach is linked to the expert involved. Despite the documentations made available (list of deliverables within the R&D process and LCA results), results may differ depending on the level of understanding of both the R&D processes and environmental aspects of the expert part of the experiment.

Another bias who could be mentioned is the level of uncertainty and the attrition rate linked to the advancement of the project. Indeed, both are usually high at the beginning and the more a project is going through the different stages, the more accurate the environmental aspects can be assessed but less environmental levers appear. This bias was indirectly considered in the approach with the number and the type of deliverables of each stage.

Nevertheless, our experiment led us to the potential contribution of the NPD stages of medicine, to the environmental aspects per lifecycle step profiles shown in Figs. 4 and 5; and the eco-design potential levers of product in Fig. 6.

5.3. Major highlights and convergence points

For R&D practitioners, we noticed a lack of understanding of eco-design approach. Even if all interviewees are aware of the environmental issues that we are facing and are convinced of the necessity to integrate environmental aspects into their activities, a lack of holistic perspective is perceivable.

Despite the three macro design steps described in chapter 4.1, we decided to present major highlights and convergence points through the four main stages described in Fig. 2 as it is commonly used in the pharmaceutical sector.

- Research

Result show that, at this stage, the objective is to identify a molecule with a possible therapeutic target and its role in the disease. Other product aspects (such as the galenic form or the packaging) are usually not studied. Nevertheless, some decisions may have some indirect impact on the rest of the lifecycle steps. For instance, for the same disease, either if the API is based on biologic or small molecule, the specifications will most likely not be similar and imply different possibilities, such as the administration mode (e.g.: one API is only stable in solution

Table 5
Breakdown of eco-design potential within the pharmaceutical NPD for the global warming impact with the aggregation of the lifecycle steps (API, formulation, packaging, distribution and use & end of life).

Research		Early development			Late development			Market	
Target identification	Lead discovery	Preclinical trials	Phase 1	Phase 2a	Phase 2b	Phase 3	Approval	First launches	LCM
6%	*13%*	*15%*	*/*[a]	*23%*	*21%*	*3%*	*10%*	*4%*	*5%*

[a] Anomaly due to no clear deliverable in the list provided to the expert.

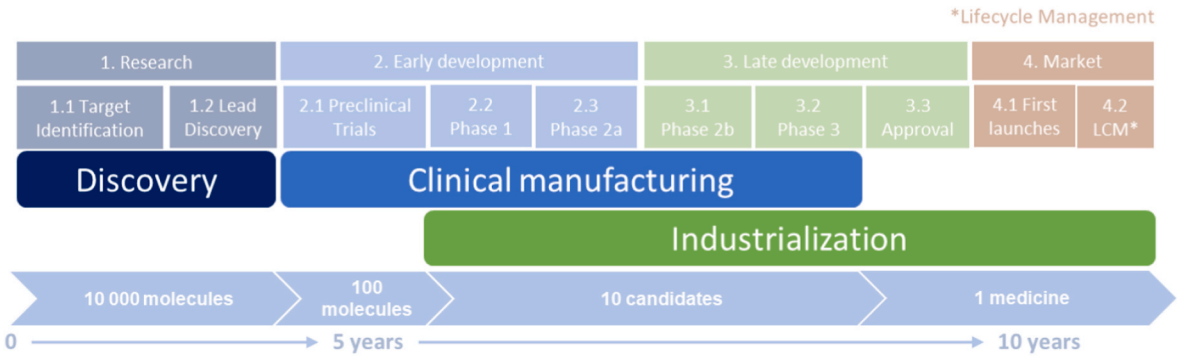

Fig. 4. The three macro design steps within the Pharmaceutical Development process.

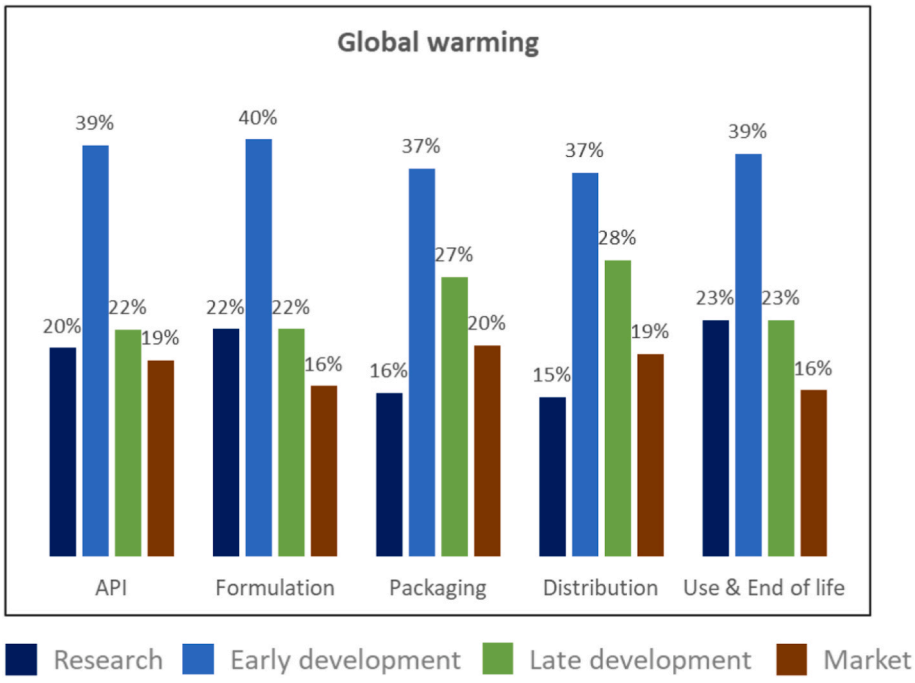

Fig. 5. Breakdown by lifecycle stage of the level of influence of the deliverables of the medicine NPD, for the global warming impact per lifecycle steps (API, formulation, packaging, distribution and use & end of life), based on 263 deliverables assessed.

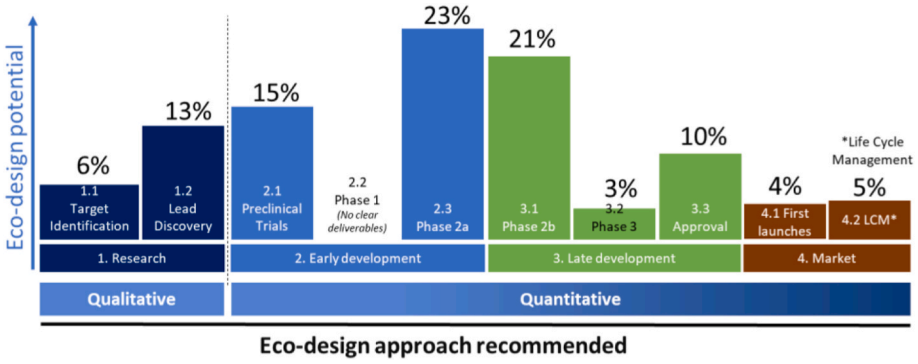

Fig. 6. Eco-design approach recommendation with the potential levers of product (average of each step of the lifecycle) per sub-step of the pharmaceutical development, for the global warming indicator.

and the other in powder, who allow to have oral forms like tablets). In this case, it will impact indirectly the galenic form of the product, related excipients and by extension, the supply chain required to manufacture the product.

We can conclude that, depending on the type of the API, the eco-toxicity profile of it may vary and lead to different environmental impacts. Nevertheless, key decisions choices for APIs begin at this stage to reduce the number of candidates. It could be an explanation of the

contribution for freshwater ecotoxicity and freshwater eutrophication profiles.

The level of uncertainty remains high and does not allow for a quantitative assessment. Some examples can be mentioned who are explaining this aspect: the high number of API candidates screened, the laboratory scale of production (which is not representative of the industrialized), the final marketed form is neither studied nor even defined yet. Nevertheless, API decision remains key for the ecotoxicity impact, and this stage should not be excluded. Therefore, a qualitative approach seems appropriate.

- Early development

The results show that the "eco-design potential" levers are mainly within this stage, when trials are conducted (clinical trials, phase 1 & 2a). During the clinical trials, the galenic form used to perform studies is not representative of the marketed product. If the molecule shows preliminary efficacy, other forms are developed for phase 1 & 2a, who are closer to the marketed product. Indeed, studies to set the specifications and to ensure safety for patients must be conducted on the final form. The packaging is not defined during this stage. As one of the main roles of the primary packaging aim to ensure the safety of patients by keeping the product stable and secure, choices of API, galenic form or even administrative route will imply ranges of packaging. As an example, liquids for injectables will not have blisters as primary packaging, unlike tablets for oral use. And on the other hand, tablets for oral will most likely not be in pre-filled syringe. With the same way of thinking, those decisions will have indirect impacts on the distribution (e.g.: storage conditions of the product, who may differ in the choice of packaging). Therefore, decisions during this stage will define most of the environmental aspects of the product.

As the validation of processes takes time, when the medicine shows some positive results in trials, industrialization steps may begin (e.g.: Scale up of processes). Therefore, evaluation of industrialization pathways may begin after the preclinical trials.

In other words, we can understand that data regarding the final marketed product begin to be generated and environmental improvements remain possible since decision making is still on going. These non-exhaustive elements may explain the importance of the early development in the decision making in terms of eco-design.

- Late development

During this stage, our study shows that the purpose of phase 2b is to study the product with a form close to the marketed one, major modifications around API or the galenic forms are usually not expected. The specifications of the product are usually frozen after phase 2b.

The industrialization choices continue to be explored (e.g.: technology for production) and some options start to be assessed (e.g.: packaging, distribution mode). At the end of this stage, every aspect of the product is defined and frozen due to regulatory constraints.

It means that in terms of eco-design, all data should be available to assess the environmental profile of the product. Nevertheless, major modification of the product cannot be performed at this stage or require another round of trials or years of studies. For instance, modification of the galenic form of a tablet to a liquid, may imply changes of the excipients. Depending on the interaction between each compound and the processes to manufacture the drug product, the physical property of the product may change (e.g.: condition of stability) and need to be assessed. Therefore, both product aspects and related activities (e.g.: industrialization, distribution), should be optimized at the end of this stage.

- Market

Right before the first launches, our results show that decision making regarding secondary and tertiary packaging may occur. Main parameters are usually fixed and due to the regulatory constraints, modifications are complex as mentioned previously.

At this stage, we can understand that, even if the level of understanding of the product is high, the levers to improve the product are small. It seems possible to fine tune some aspects, but most of the effort should be deployed in other stages.

The figure below summarizes our eco-design recommended approaches to adapt with every sub-step of the pharmaceutical NPD.

6. Conclusion

One of the main societal duties of the pharmaceutical sector is to provide medicines. As defined by the SDG three, they need to make them available and affordable in order to grant good health, despite the inequities all around the world. But this responsibility does not allow the pharmaceutical industry to avoid the environmental concerns related to its activities and products. Nowadays, environmental risk assessments are performed. Nevertheless, this approach does not provide a holistic view of the environmental impact of the product and is not based on a lifecycle perspective. Eco-design is an approach which can support industries to consider them. Trace of environmental approaches integrated into design can be found around 1960, but the field of eco-design research seems to be formalized in the 1990's Despite the effort of the pharmaceutical industry to consider environment aspects), the literature suggests that this sector seems to struggle when it comes to have a holistic approach of eco-design into the medicine NPD process.

Therefore, the research question *"In which steps of the pharmaceutical R&D process is there sufficient information available to* support *eco-design activities?"* was raised in this paper. We tried to focus on the meso level of the integration of eco-design as described by Brones. To answer this question, we performed two experimentations in order to feed our two hypotheses; *H1* "*Eco-design activities can be focused on specific steps of the medicine NPD"; H2 "Quantitative environmental assessment, such as LCA, can* support *decision making during the Pharmaceutical NPD"*. We have found that information is available at each stage of the R&D process that could support eco-design activities, but quantitative environmental assessments would only be possible in the later stages due to high uncertainty in the data available during the research and early development stages.

The first experimentation consisted of semi-directive interviews of 10 practitioners of the pharmaceutical R&D. The second one was an investigation performed with both LCA results of an existing medicine and R&D process & related deliverables. The aim was to identify eco-design potential levers & decision-making during medicine NPD process. This last one was not yet explored in the literature, and we proposed to have a first case within the pharmaceutical sector.

Results show that, even if unknowns and uncertainties regarding the specificities of the product remain in the research phase, the environmental levers are high, and an eco-design approach should not be excluded. At the early development, characteristics of the product and industrialization start to be investigated. Therefore, a focus on eco-design seems to be appropriate. At the beginning of late development, eco-design levers still are relevant but seem to decrease exponentially until the market. The key focus of eco-design within the pharmaceutical R&D seems to appear between the early development and the late one. In other words, between clinical phases 2a and 2b. Therefore, the *H1* "*Eco-design activities can be focused on specific steps of the medicine NPD"* seems to be validated.

Even if eco-designers can be identified during the whole pharmaceutical development, the level of understanding of the final form marketed is not the same at each phase. It is therefore not possible and does not seem relevant to have a quantitative environmental assessment at each phase. The *H2 "Quantitative environmental assessment, such as LCA, can* support *decision making during the Pharmaceutical NPD"*, is therefore not fully validated but could be rectified by the possibility to

engage eco-design qualitative or quantitative approaches, all along the NPD. Due to the lack of data during research, quantitative approach cannot be initiated. Nevertheless, linked to the environmental potential levers, qualitative approaches are strongly recommended to support the medicine NPD as the decision making will have indirect impact in the rest of the development (e.g.: administration route will impact the galenic form). The quantitative approach should start at the beginning of the early development until the market. The maximum eco-design potential seems to be between phase 2a and 2b.

7. Future work

Medicines are complex products and development specificities (e.g.: small molecules, biologics) are not explored in this paper. This study could be fostered with interviews of other experts, to better represent both R&D process and practices in other pharmaceutical industries. The second experiment could gain in deepness by integrating not only other different environmental experts but also practitioners of pharmaceutical development.

The integration of eco-design should include the macro part, the meso, the micro and the soft side. In this paper, we focused on the meso level, and we showed that it is possible to integrate eco-designers all along the medicine NPD with qualitative or quantitative approaches. To foster the meso level, it seems necessary to identify the types and the levels of environmental requirements per phase.

Another perspective should be to work on the micro level, or in other words, tools to support the eco-design approaches. Both tools to support assessment and improvement could be fostered. For instance, few Product Category Rules are available for pharmaceutical products (Emara et al., 2018; Jiménez-González and Overcash, 2014; Martin et al., 2022). It is therefore complex to adopt a harmonized approach of LCA without such documentation formalized. As the LCAs are time-consuming and complex to handle, simplified models to foster the environmental assessment could be proposed for R&D experts (Suppipat et al., 2021). The model should integrate the level of uncertainty, who most likely will depend on the phase of the pharmaceutical development. A more technological approach could also be a way to foster eco-design. For instance, the opportunities offered by the industry 4.0 could ease the data collection for LCA (Dahmani et al., 2022; Ding, 2018; Garcia-Muiña et al., 2019; Gupta et al., 2021).

For improvement tools, it could be interesting to develop guidance for R&D practitioners. As an example, for galenic formulators, if they need a film coating for a tablet, a list of excipients with this function could be proposed with their related environmental impacts. The development of model to generate optimal solutions through the LCA approach can be an opportunity to guide the development teams (Tao et al., 2018). The circular economy concept is already known is the pharmaceutical sector, especially when we talk about solvents and catalyzers. Nevertheless, this approach could be fostered in the whole Lifecycle of the product and coupled with the LCA to make sure of the environmental benefit of closing loop and therefore support the viability of medicines (Aguiar et al., 2021; Ang et al., 2021; Dumée, 2022; Hobson, 2021).

Finally, the macro level and the soft side of eco-design was not part of this paper. The macro piece is intrinsic of each company, and they should integrate eco-design in their strategy (e.g.: clear targets for every level of the organization). The soft side is focused on people and behavior. It is therefore recommended to adapt the eco-design management approach to the company's culture and by considering the changes resistance (Boks, 2006).

CRediT authorship contribution statement

Duc-Nam Luu: Conceptualization, Methodology, Writing – original draft, Visualization, Investigation. **Hervé Gachet:** Formal analysis. **Claus-Jürgen Maier:** Project administration, Validation, Writing – review & editing. **Nicolas Maranzana:** Supervision, Writing – review & editing. **Améziane Aoussat:** Supervision, Writing – review & editing.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclepro.2022.132785.

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