Proposition et formalisation d'un modèle méthodologique pour la mise en place d'une stratégie d'éco-conception ainsi que des outils de déploiement pour son implémentation. Application au domaine de la pharmaceutique

Duc-Nam Luu

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Duc-Nam Luu. Proposition et formalisation d'un modèle méthodologique pour la mise en place d'une stratégie d'éco-conception ainsi que des outils de déploiement pour son implémentation. Application au domaine de la pharmaceutique. Génie des procédés. HESAM Université, 2023. Français. NNT : 2023HESAE033 . tel-04496067

HAL Id: tel-04496067

https://pastel.hal.science/tel-04496067

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HESAM UNIVERSITÉ

Arts et Métiers Institute of Technology

ÉCOLE DOCTORALE SCIENCES DES MÉTIERS DE L'INGÉNIEUR
Laboratoire de Conception de Produits et Innovation – Campus de Paris

THÈSE

présentée par : **Duc-Nam LUU**

soutenue le : **26th, June 2023**

pour obtenir le grade de : **Docteur d'HESAM Université**

préparée à : **École Nationale Supérieure d'Arts et Métiers**

Spécialité : **Génie industriel**

Proposal and formalization of a methodological model for the implementation of an eco-design strategy.

Application to the pharmaceutical industry

THÈSE dirigée par :
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THESIS

Acknowledgements

This doctoral thesis is formalizing three years of research, but it is also a marker of my journey in the pharmaceutical industry. I would like to dedicate this work to all the people that contributed, directly or indirectly, from a scientific, professional, and personal perspective. To these people who supported me all along this journey, and made me grow, as the human being that I am today.

I would like to start with the members of the jury, Pr. LE CARDINAL, Pr. ZWOLINSKI, Pr. GARDONI, for their analysis, commentary, and patience during the evaluation of this work.

I thank the Pr. Améziane AOUSSAT, Director of this doctoral thesis, who let me the chance to integrate the LCPI for an Eco-design PhD. I will always remember this phone call at the end of my engineer second year where you gave me advice and agreed to support me for this PhD journey. I also thank Dr. Nicolas MARANZANA for his support, trust, and exchanges to explore unknows.

In the LCPI, I would like to thank the overall researcher team (Patrice DUBOIS, Camille JEAN, Fabrice MANTELET, Marc LE COQ, Vincent MEYRUEIS, Frédéric SEGONDS) for the remarks, questions and advice during the GTT. To the administrative and technical teams, Séverine FONTAINE, Valérie SAFFAR, Bernard AUBAGUE, Hélène ZIMMER, Pierre VEDEL, and Benoît SCHAEFFER, without you, thank you for the support provided.

I do not forget the now PhDs and PhDs student! It was great to share with you these particular moments that we are facing in a doctoral thesis; (some) ups and (a lot of) downs but always with a positive energy. The double Armand (LANG & HUET), Antoine FEUGIER, Chawki EL ZANT, Clara GANDREZ, Arava SANDFORD, Eliot GRAEFF, Annelinne LETARD, you all were examples to follow. Sylvia IMBART and Edouard BOYAULT, I will be the last one from the three of us to end my PhD! To Edouard, *"spéciale dédicace"* to our special *"binôme"*. Who would know that helicopter and medicine would be so efficient! To the generation of LCPI PhDs after us, Quentin CHARRIER, Marine CATEL, Jean-René CAMARA, Tristan BRIARD, good luck! I do not forget you, Simon MASSOT. Hope your PhD will not be the next episode of my PhD but your own one.

During this PhD, I was able to meet several environmental experts from Quantis. I thank all of them for their time and discussions that we had. Dimitri CAUDRELIER, Anne DESERABLE, Sebastien HUMBERT, and more particularly Pierre COLLET, Auriane BODIVIT, Noémie LEVE, Jean-Baptiste BAYART, many discussions always fruitful.

My pharmaceutical journey before this PhD and my engineer degree. That's why I would like to thank a lot of people before my now former colleagues from Sanofi (sorry 'bout that). *Un grand merci à mes enseignants de BTS Chimie du lycée d'Arsonval, sans qui rien n'aurait vu le jour. Jeanne-Laure DORMIEUX et notamment Christophe HONNORAT. Merci pour cette discussion après un cours, où j'hésitais à quitter la formation. Merci à l'équipe de l'ETSL, Didier STUDER, éternel pilier de cette école, et Isabelle LOISEAU, véritable soutien pour les étudiants. Même des années après la Licence, j'ai pu compter sur vous pour me soutenir dans le démarrage de la thèse. Merci au CNAM et particulièrement Sylvie BALTORA, bien qu'ayant eu des hauts et des bas, je suis profondément reconnaissant pour l'aide apporté. Un immense merci au laboratoire Synth-innove, à François SCHERNINSKI et son équipe, pour m'avoir accueilli lors de mon premier apprentissage en Licence. Il me semble que cela a été le point de départ de cette aventure. Florent COUSIN, plus qu'un collègue, merci pour ton éternel soutien.*

After seven years in Sanofi, I cannot forget to thank my former colleagues. But for sure I will miss some of you.

To all Sanofi employees that I was able to meet, collaborate with, or even just discuss, a big thank you. Elise PAPE, Julie MacDONALD, Ron DICOLA, Maria VAN DE PEER, Yves BERGHMANS, Dirk GERSTING, Christian POMMEREAU, and so many and countless people that I can't list here. The site visits, (like Aramon, Sisteron, Marcy l'étoile, Val de reuil, Vitry, Frankfort, Geel, Ghent, and the others) were always priceless, from a professional view to better understand the ways of working & processes, but more importantly from a human perspective. It confirmed to me that the real strength of Sanofi is not about its product portfolio or its infrastructure. It's all about the collaborators.

At the Global HSE, thanks to all for the positive energy and support during the four years with you. Special thanks to / for: Hervé PENET / laughs and the "behind the scenes" insights; Benoît BARUTEAU / support from a real Gadzart to a fake one.

Obviously, thanks to the Global environmental team. Thanks Jose-Francisco VALLEJO CARRERA for the advice, good luck with the new team! Peter WILSON, Jennifer TRAVIGLIA, Camille COTTIN, for your energy. Maurice AUGUSTE (sorry you were not the first one and not the last one), thanks for the support. Often borderline, but always like *"une mère poule"* with interns. Romain JOURNEL, I really enjoyed the discussions and the time we were able to work together. Hope we will be able to jam one day. To Alain GOASGUEN, one of my Sanofi mentors, thank you to have believed in me.

To the Eco-design team of Sanofi, which is part of the Global environmental team BTW. Achille LAURENT, all the things I know in LCA, I owe it to you. I cannot express how grateful I am for that. Sarah-Arias ZEBALLOS, it was a pleasure to collaborate with you. I still want to see these Sanofi Belgium lamas that we were not able to meet during our road trip! And of course, two of the four mentors I had in Sanofi. To Hervé GACHET, you already know it, nothing would have been possible without you. From this coffee talk where we decided to launch this PhD journey, to the work we performed for our paper and more. Also, somewhere between, unspoken things! To Claus-Jürgen MAIER, and the two years support you provided. I grow as scientist, but also as human being thanks to you, *danke schön*.

To my former Amilly colleagues, where I was born as Sanofi employee. *Je suis dans le regret de vous annoncer que je ne suis plus « le plus vieil alternant de Sanofi » (voir de France pour certains). Trop de personnes à remercier sur le site, et j'en oublierai sans doute. Malgré tout et de manière non exhaustive, Julie DELION, Sylvain BAUDEQUIN, Alexandre TEIXEIRA, Julien CHARTIER, Julia FLAUDER, Flora FAURE, Rémy MOULIN, Ludovic FLE… Sans vous, Amilly n'aurait pas été la même chose. Sébastien BERTALOT, toi qui es parti trop tôt, j'espère avoir gardé le sens des réalités en ne devenant pas un énième « c** du central » comme tu disais. Evidemment, je ne peux pas ne pas remercier l'équipe HSE. Mon premier mentor chez Sanofi, Vincent LAILHEUGUE. Merci d'avoir cru en moi et d'avoir été assez fou pour engager un musicien dans ton équipe. A Franck DESPLANCHES, Claire KERNANEC et Laurent BOUVRY, merci pour votre soutien et vos connaissances. A Marie-Ange COMPIN, merci pour ta gentillesse, ne change pas. A Mauricette TRAINOIR, la maman du service, j'espère que la retraite de t'épuise pas trop ! A Fateh AMOKRANE, le « grand frère », je saurais me souvenir de ce que t'as fait. Toi et moi on sait !*

A Léo-Paul LUTON et Mamady TOURE, merci pour cette « coloc » en école d'ingé. Ces années resteront bien ancrées. Roman TEDESCHI, qui aurait cru après le CIM que les chemins de la vie m'amèneraient ici ?

Enfin, j'aimerai remercier ma famille. A ma mère et Sylvain, qui ont et seront toujours présent pour nous, leurs enfants. A ma tante Di-ba et Jean-Louis, respectivement ma deuxième mère et mon troisième père. Giac, ma fausse jumelle, merci de m'avoir supporté pendant 33 ans et plus à venir. Erwin, je serais finalement le premier Docteur de nous deux. A l'ensemble de ma famille, côté PHAM et côté LUU, merci à tous pour votre soutien qui compte tant pour moi. A Camilla, qui m'a supporté pendant ces quatre ans, dont trois ans de thèse. Sans parler de la phase de rédaction de manuscrit…

Finally, thanks to the brave that are reading those lines and this manuscript. I hope the work formalized here will help you in your work, answer some questions and raise more, to feed your thoughts. In any case, I would be delighted to discuss about it with you! Have a nice read.

To my father / A mon père / Kính tặng người cha yêu quý của con

Résumé

Les enjeux environnementaux prennent une place majeure au sein de nos sociétés modernes. L'activité Humaine contribue à la dégradation de l'environnement et les industriels ont le devoir de limiter l'impact des solutions qu'ils proposent et mettent sur le marché. L'éco-conception est une des démarches de la conception pour le développement durable qui permet d'intégrer les aspects environnementaux en amont, lors des phases de développement. La pénétration de ses pratiques au sein d'industriels nécessite une intégration verticale et horizontale. L'intégration horizontale concerne les aspects stratégique, tactique et opérationnels tandis que l'intégration horizontale focalise sur les aspects de changement culturel et de facteurs humain. Cette thèse de doctorat s'intéresse à l'intégration de l'éco-conception au sein d'une entreprise multinationale pharmaceutique. L'objectif du projet s'est attaché à venir formaliser les concepts pour cette intégration dans l'industrie pharmaceutique afin de soutenir la transition des pratiques interne de ce secteur. La variété et complexité des aspects de l'éco-conception, ainsi que les défis à la fois techniques et organisationnelles de l'industrie pharmaceutique doivent être pris en compte afin de fournir une approche de transition cohérente. Les expérimentations de ces travaux ont été menées avec un partenaire, industriel pharmaceutique à l'échelle internationale, en collaboration avec les Arts et Métiers, campus de Paris. Les travaux menés ont permis de poser les bases d'un modèle d'intégration de l'éco-conception au sein de l'industrie pharmaceutique, avec des outils d'accompagnement associés.

Mots clés : Eco-conception, Industrie pharmaceutique, Modèle d'intégration, Environnement

Summary

Environmental issues take a major place in our modern societies. Human activity contributes to the degradation of the environment and manufacturers have the duty to limit the impact of the solutions they offer and put on the market. Eco-design is one of the approaches of Design for Sustainability which makes it possible to integrate environmental aspects, during the development phases. The penetration of its practices within industrials requires vertical and horizontal integration. Horizontal integration concerns the strategic, tactical and operational aspects while horizontal integration focuses on the aspects of cultural change and human factors. This doctoral thesis focuses on the integration of eco-design within a multinational pharmaceutical company. The objective of the project was to formalize the concepts for its integration in the pharmaceutical industry in order to support the transition of internal eco-design practices in this sector. The variety and complexity of eco-design aspects, as well as both the technical and organizational challenges of the pharmaceutical industry must be taken into account in order to provide a coherent transition approach. The experiments for this work were carried out with a partner, an international pharmaceutical industry, in collaboration with the Arts et Métiers, Paris campus. The work carried out has made it possible to lay the foundations of an eco-design integration model within the pharmaceutical industry, with associated support tools.

Key words: Eco-design, Pharmaceutical industry, Integration model, Environment

Summary

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List of acronyms and abbreviations

ACS	American Chemistry Society
AM	Health insurance (Assurance Maladie)
ANSM	National agency for the safety of medicines (Agence National de la Sécurité du Médicament)
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical classification
BoM	Bill of Material
CEPS	Committee of health products (Comité Economique des Produits de Santé)
CIP	Cleaning In Place
CMC	Chemistry, Manufacturing, and Controls
COC	Cyclic Olefin Copolymer
COP	Cyclo-Olefin-Polymer
CSR	Corporate Social Responsibility
DEimeter	Drug Eco-designed integration meter
DRM	Design Research Methodology
DfS	Design for Sustainability
EA	Environmental Assessment
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EPD	Environmental Product Declaration
EphMRA	European pharmaceutical Marketing Research Association
ERA	Environmental Risk Assessment
EU	European Union
FDA	Food and Drug Administration
FU	Functional Unit
GHG	Greenhouse Gas
HAS	High authority of health (Haute Autorité de Santé)
HCP	HealthCare Professional
ICH	International Council for Harmonization of technical requirements for pharmaceuticals for human use
IPCC	Intergovernmental Panel on Climate Change
ISPE	International Society for Pharmaceutical Engineering
LCA	Life Cycle Assessment
LCIA	Life Cycle Impact Assessment
LCM	LifeCycle Management
LCPI	Laboratoire Conception de Produits et Innovation (Product Design and Innovation Laboratory)
mAbs	Monoclonal antibodies
Mt or MT	Megaton = 1000 tons
NDA	New Drug Application
NE	Novel entities
NGO	Non-Governmental Organization
NHS	National Health Service
NIH	National Institute of Health
NME	New Molecular Entity

NPD	New Product Development
OTC	Over the Counter
PBT	PolyButylene Terephthalate
PC	PolyCarbonate
PCR	Product Category Rule
PE	PolyEthylene
PEC	Predicted Environmental Concentration
PEF	Product Environmental Footprint
PET	PolyEthylene Terephthalate
PFS	Pre-Filled Syringe
PNEC	Predicted No-Effect Concentration
POM	PolyOxyMethylene
PP	PolyPropylene
R&D	Research and Development
SDGs	Sustainable Development Goals
SIP	Sterilization In Place
SMR	Medical benefit (Service Médical Rendu)
TBL	Triple Bottom Line
UK	United Kingdom
UN	United Nations
UNCAM	Union of insurance group (Union Nationale des Caisses d'Assurance Maladie)
UniHA	Union of Hospitals for Purchasing
US	United States
WHO	World Health Organization

General introduction

From the apothecaries, who were providing products to heal, to the current big pharma who are providing both mass production drugs or specialty care ones, medicine have played a key role in our modern society (Bhugra, 2014). The intrinsic role of the pharmaceutical industry is nowadays to make medicines available (Gateaux and Heitz, 2008) and affordable (Nussbaum, 2009) to contribute to the well-being and health of the Humankind.

The United Nations (UN) have estimated the worldwide Human population at 7.9 billion for 2021 and was estimated around 2.5 billion in 1950 (UN, 2022). The projections estimated a demographic stabilization between 2050 and 2075 to reach around 10.5 billion of living being. Discrepancy in healthcare is an issue not solved nowadays. The COVID-19 vaccination is a perfect witness of the difficulty to provide healthcare in different countries (Sen-Crowe et al., 2021). The growing population will most likely add challenges to the supply of medicines products. Its emphasis a first social difficulty of the pharmaceutical sector.

Additionally, the Earth is currently facing an environmental crisis with never encountered proportion. Formalized by the Planetary boundaries (Persson et al., 2022; Rockström et al., 2009; Wang-Erlandsson et al., 2022), on nine thresholds that shouldn't be exceeded to live on a proper Earth, five of them are exceeding their limits. The concept of Country overshoot day is also formalizing the fact that the way of living of most Human is not sustainable in regards of the resource regeneration capacity of the planet (Global Footprint Network, 2022).

To address the environmental crisis, the international community, through the UN, had formalized the Sustainable Development Goals (SDGs) in 2015, where some of them are related to the environmental aspects (UN, 2015). Some instance and organizations are also known to contribute to the debate such as the COP (Hussain and Mahase, 2022) or the Intergovernmental Panel on Climate Change (IPCC) (Rama et al., 2022).

Like any Human activity, the pharmaceutical industry is not neutral in terms of environmental impact. In regards of the Climate change, the literature suggest that the pharmaceutical industry is contributing between 3% and 33%, with a most likely value around 15% of the Greenhouse Gas (GHG) emissions of the health care systems (Eckelman et al., 2018; Lenzen et al., 2020; NHS, 2022; The Shift Project, 2021). But the environmental footprint is not limited to the GHG emissions, and pharmaceutical product do have environmental impacts in other aspects such as, non-exhaustively, the resource consumption (Luu et al., 2021), the degradation of water (Wilkinson et al., 2022) or even on the human-health (Souza et al., 2019).

This last element represents a high paradox of the pharmaceutical industry. By making available medicines products, they are contributing to improve the health of population. But in the other hands, by producing such products, they are polluting the environment. Therefore, take into account the environment is a key factor for this sector, especially with the One Health concept philosophy (Destoumieux-Garzón et al., 2018).

Nowadays, the pharmaceutical perform Environmental Risk Assessment (ERA), to determine the environmental fate of their Active Pharmaceutical Ingredient (API) (Manuilova, 2003). Since decades, they also adopted the Green chemistry approach, in order to reduce the environmental burden of their manufacturing processes (Anastas and Williamson, 1996; Diorazio et al., 2021). However, these approaches are lacking holistic perspective, both in terms of environmental footprint and lifecycle understanding.

The community of Design engineering is working since the 1990s on Design for Sustainability approaches (Ceschin and Gaziulusoy, 2016). The Eco-design approach is one of them and focus on the environmental dimension of the Sustainability. By integrating the holistic environmental footprint, in a lifecycle perspective, into the design of product or service (EEA, 2001), the Eco-design is one approach to decrease their environmental burden. However, this mindset is not yet well implemented within the pharmaceutical sector.

To address these challenges, this doctoral thesis involves transdisciplinary expertise, with a partnership between Sanofi and the Product Design and Innovation Laboratory (Laboratoire Conception de Produits et Innovation, LCPI, EA 3927), part of the Arts et Métiers Institute of Technology.

In this context, the research aimed to support the pharmaceutical industry in the Eco-design journey. Through the state of the art performed on several topics such as the engineering science, the Eco-design, and the pharmaceutical industry, success factors and barriers to Eco-design products were identified. This allowed us to structure our research with the problematic: ***"How to foster the Eco-design practices into the New Product Development of medicines in a systemic way?"***.

Two hypotheses are formalized to structure our research.

The first one is based on an organizational perspective. The literature mentions the integration of environmental aspects into decision making of the development process as one key success factor of an Eco-design journey. The second hypothesis is built around an operational view. Eco-design tools are available in the literature and the adaptation of them could favorize the Eco-design appropriation of the pharmaceutical industry.

The work performed during the doctoral thesis are presented in this manuscript in four phases.

- Phase 1: Context presentation, stakes of the work and state of the art
- Phase 2: Formalization of the problematic, linked to the findings of the state of the art, and hypothesis of resolution
- Phase 3: Description of the work performed during the PhD who aimed to feed the hypothesis
- Phase 4: Summary of contributions, limits, conclusions, and perspectives

Those four phases are structured in nine chapters, which aim to describe the way of thinking all along this research.

Chapter I: Context of the work (Phase 1)

The first chapter aim to present the overall context of the research. The context linked to the international community, the pharmaceutical industry, the scientific, and the laboratory are presented. This chapter set the position of this research within each of these dimensions.

Chapter II: State of the art (Phase 1)

The second chapter set the state of the art on key related topics of this research. Main concepts of Design science and engineering, the Design for Sustainability, Technical aspects of Medicines, and Environmental perspectives of pharmaceutical products are exposed. Those elements constitute the scientific foundation of this research.

Chapter III: Problematic and hypothesis (Phase 2)

The observations drawn from the state of the art are synthesized in chapter three to lead to the formalization of the research problem guiding this doctoral thesis. The methodological approach aimed at resolving this is then presented and leads to the emergence of the two hypotheses structuring this research work.

Chapter IV: Stakeholders management (Phase 3)

The consideration of external stakeholders is identified as a success factor to implement an Eco-design approach. The first experimentation of this research aimed to identify a framework of external stakeholders of the pharmaceutical industry, to consider in Eco-design approach.

This work was based on both literature review and workshop with experts of the pharmaceutical industry, in close contact with their external stakeholders. A first theoretical framework is proposed and another one based on experimentation was set. The experimental one was structured based on the Geels framework of stakeholders to considers when innovating (Geels,

2006). A prioritization of these stakeholders was set during the experimentation. This work emphasis the evolving considerations of these stakeholders, linked to both societal pressure and level of external stakeholders understanding of environmental issues of medicines. This last aspect highlights the need of the pharmaceutical companies to consider the holistic environmental footprint of their products, in a lifecycle perspective.

Chapter V: Pharmaceutical design process (Phase 3)

The chapter five focus on the long journey of developing a pharmaceutical product. It highlights the sequential process, which is regulatory driven, to ensure the safety of the patient.

Eco-design approaches should be set to the phase of the process. To identify relevant Eco-design levers within this process, two experimentations were performed. A first one, based on interviews of Research and Development (R&D) practitioners and a qualitative assessment was performed in parallel. The results were then merged to define convergence points and set an overall framework regarding the Eco-design potential levers within the pharmaceutical design process.

This approach is the first step in order to be able to reach a systemic approach of Eco-design.

Chapter VI: Eco-design maturity model (Phase 3)

Despite the numerous tools available in the literature, the pharmaceutical industry struggle to implement in a systemic manner Eco-design approaches. After we proposed our mapping of Eco-design potential within the development process, it appeared to us that R&D practitioners needed support to be able to implement the Eco-design mindset within their activities.

This chapter aimed to present the development of an Eco-design maturity model tool, dedicated to the pharmaceutical industry: the Drug Eco-designed integration meter (DEimeter). The development was based on the Design Research Methodology (DRM). The aim of this tool is to track and guide the Eco-design practices within R&D. It is structured through two dimensions, the organizational and the operational one. The first dimension, the organizational, aimed to track from a management perspective the practices aligned with an Eco-design approach. The operational dimension proposes tools to use, adapted to the phase of the development.

Chapter VII: Monoclonal Antibody LCA guidance (Phase 3)

Life Cycle Assessment (LCA) is currently considered as one of the best tools to assess holistically the environmental footprint of products and services, from a lifecycle perspective. The application of the methodology behind this tool is not mature within the pharmaceutical sector and is time-consuming.

The aim of this chapter is to provide guidance when performing an LCA for monoclonal antibodies (mAbs). After presenting generic and technical aspects of mAbs, recommendation to perform LCA for such products are made, based on a study done during the research. Such recommendations could be the first elements to build a Product Category Rule (PCR) for mAbs, and therefore foster the capacity to assess this family of product.

Chapter VIII: Contributions and limits (Phase 4)

Chapter seven highlights the contributions made during this research. Both description and limits are presented to set an overall picture of the work of this research.

Chapter IX: Conclusion and perspectives (Phase 4)

The chapter nine summarizes the work presented in this manuscript and recontextualizes it to bring out the contributions and the perspectives that they underlie. A set of questions remaining to be solved is finally raised to feed the pursuit of scientific reflections on the integration of Eco-design within the pharmaceutical industry.

The figure below summarizes the links between the four phases and the nive chapters.

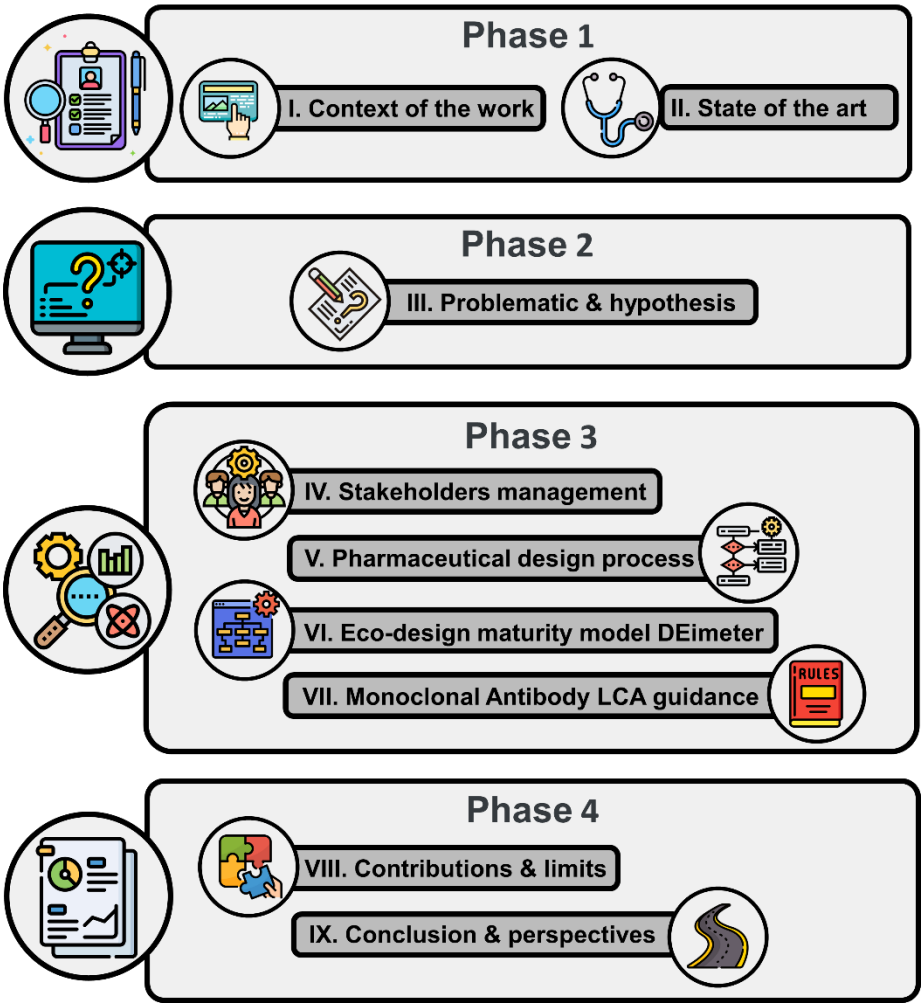


Figure 1 - Summary of the nine chapters of this manuscript within the four phases

Phase 1

Chapter I

Context of the work

« Une croissance indéfinie est impossible, nous n'avons qu'une seule Terre, mais une civilisation du bonheur est possible »
Dumont, R., 1974. La campagne de René Dumont et du mouvement écologique: Naissance de l'écologie politique. Déclarations, interviews, tracts, manifestes, articles, rapports, sondages, récits et nombreux autres textes. FeniXX.

"Infinite growth is impossible, we only have one Earth, but a civilization of happiness is possible"
Dumont, R., 1974. La campagne de René Dumont et du mouvement écologique: Naissance de l'écologie politique. Déclarations, interviews, tracts, manifestes, articles, rapports, sondages, récits et nombreux autres textes. FeniXX.

I Context of the work

This chapter aim to present the context of this work, by presenting succinctly General elements, linked to the international community, the Industrial context, with some historical facts and current trends, the Scientific context, the Research laboratory one to then expose main stakes of the work.

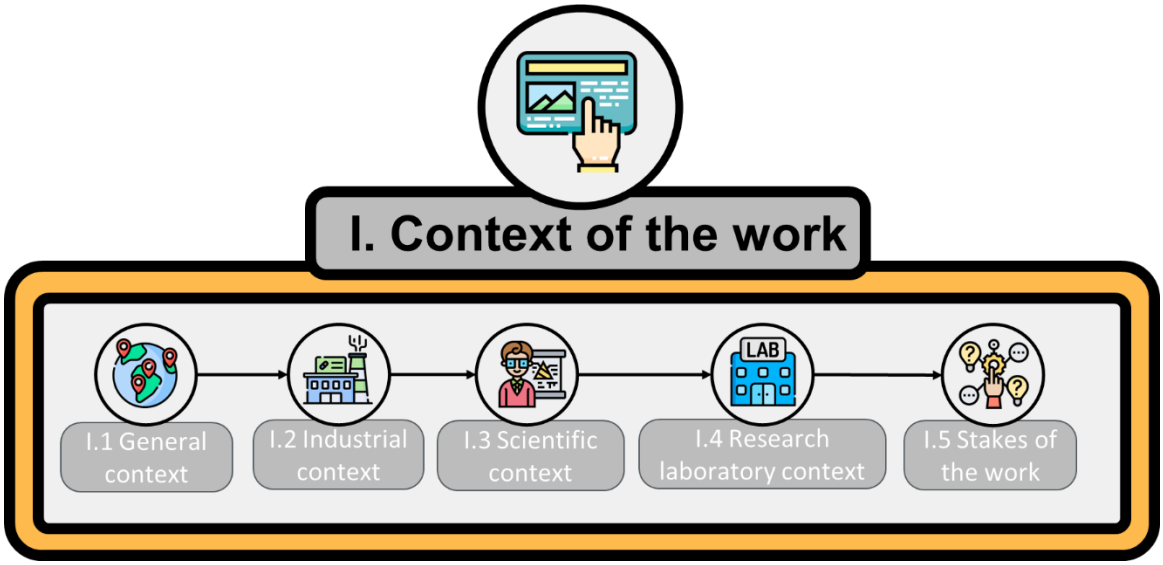


Figure 2 - Context of the work structure

I.1 General context

In 2019, the population on Earth was evaluated around 7.7 billion. The forecast of the United Nations (UN) is expecting for 2050 around 9.7 billion and 11 billion living souls for 2100 (UN, 2019). The same year, a global study highlighted that 369 diseases and 87 risk factors were identified within 204 countries (Vos et al., 2020).

Meanwhile, we are living on a planet with limited resources. In 2021, the Earth Overshoot Day, also known as the evaluated date, when the Human activities consume more than what the Earth can regenerate in one year, was determined on July 29th (Global Footprint Network, 2021). Furthermore, there is now a consensus within the scientific community to say that Human activities has warmed the climate with a peak during the last 2000 years (IPCC, 2021).

Embraced by the International community since 2015, the Environment protection is part of the Sustainable Development Goals (SDGs). 17 goals were settled in 2015 with the aim to cover all aspects of sustainability all around the world (Fleming et al., 2017).

Table 1 - List of the Sustainable Development Goals (SDGs) of the United Nations (UN)

	Title	Description
	No poverty	End poverty in all its forms everywhere
	Zero hunger	End hunger, achieve food security and improved nutrition and promote sustainable agriculture
	Good health and well being	Ensure healthy lives and promote well-being for all at all ages
	Quality education	Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
	Gender equality	Achieve gender equality and empower all women and girls
	Clean water and sanitation	Ensure availability and sustainable management of water and sanitation for all

	Affordable and clean energy	Ensure access to affordable, reliable, sustainable and modern energy for all
	Decent work and economic growth	Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
	Industry, innovation and infrastructure	Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
	Reduced inequalities	Reduce inequality within and among countries
	Sustainable cities and communities	Make cities and human settlements inclusive, safe, resilient and sustainable
	Responsible consumption and production	Ensure sustainable consumption and production patterns
	Climate action	Take urgent action to combat climate change and its impacts
	Life below water	Conserve and sustainably use the oceans, seas and marine resources for sustainable development
	Life on land	Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
	Peace, justice and strong institutions	Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
	Partnerships for the goals	Strengthen the means of implementation and revitalize the global partnership for sustainable development

Generally, the sustainability topic is part of the Corporate Social Responsibility (CSR) of an industrial. The concept of Triple Bottom Line of Elkington (TBL) (Elkington, 1998) is sometimes considered as the origin of the modern CSR. Latapí Agudelo et al. described a history and evolution of the CSR and found older trace of this concept in 1953 (Latapí Agudelo et al., 2019).

The TBL, with the People, Planet & Profit framework, can be considered as a link between the sustainability field and the CSR (Oliwa, 2021). The SDGs of the UN can be placed into the TBL framework as below.

- People: SDG 2; 3; 4; 5
- Planet: SDG 13; 14; 15
- Profit: SDG8; 9; 11

It is also possible to identify some SDGs on the crossroad of two pillars of the TBL:

- People / Planet: SDG 6
- People / Profit: SDG 1; 10
- Planet / Profit: SDG 7; 12

Finally, the SDG 16 and 17 can be understood as transversal goals, which are not directly contributing to the TBL, but are required to be able to foster them.

Figure 3 - The SDGs of the UN within the Triple Bottom Line framework

This diversity of goals highlights a well-known challenge within the Environmental ethic topic between the Anthropocentric, the Biocentric and the Ecocentric philosophies. Indeed, it raise the question of what is morally acceptable in terms of Environmental burden VS Societal contribution for the Humankind. The Anthropocentric way of thinking can be defined as *"the belief that there is a clear and morally relevant dividing line between humankind and the rest of nature, that humankind is the only principal source of value or meaning in the world"* (Purser et al., 1995). In this perspective, *"nature has moral consideration because degrading or preserving nature can in turn harm or benefit humans"* (Kortenkamp and Moore, 2001). While Biocentrism is identified as the *"ethics that sees inherent value to all living things"*, Ecocentrism go further by considering also *"environmental systems as wholes, and their abiotic aspects"* (Kopnina et al., 2017).

For a designer and more broadly the Society, the answer to the question "Is my product Sustainable?" will differ depending on his Environmental ethic. Some examples in part I.2 let us think that we are still in an Anthropocentric world, even if the Ecocentrism philosophy seems to be growing within the Society.

The purpose of this thesis is not to focus or neither discuss about the environmental ethics and philosophies. We will not initiate this important debate, closely linked to our topic, and will focus more on how the pharmaceutical sector can embrace the Environmental sustainability of its products and activities, in a holistic perspective, to contribute to the environmental journey of the Humankind.

I.2 Industrial context

The pharmaceutical industry is closely linked to the history and evolution of medicine. In this part, I aim to present a quick overview of the genesis & current trends, the societal duty, and high-level environmental aspects of this industry.

Genesis of pharmaceutical industry to current trends, a quick history

The history of products to heal or cure patient come alongside with the humankind. 5000 years (Kelly, 2010) ago, the Sumerian clay slab from Nagpur were already suggesting use of medicinal plants. Authors suggest that China, 2500 before Christ, already had 365 drugs (Petrovska, 2012) and many examples can illustrate the use of plants to heal patients. But those approaches are far from an

industrial way of production and the modern pharmaceutical industry is linked to the European history of medicine.

The history of the western pharmaceutical industry can be identified in four phases: 1870 – 1930; 1930 – 60; 1960 – 80; 1980 – present.

- *1870 - 1930*

The birth of the pharmaceutical industry is usually identified in the nineteenth century (Malerba and Orsenigo, 2015). This industry is considered as the merge of the apothecaries, who went from small production in a broader one, and of chemical companies. Usual medicines used in 1800s include opium, morphine, phenacetin and acetanilide as painkillers. Opium was also used for diarrhea and cough (Memon, 2022). Cocaine was used for oral pains and toothache as illustrated in the figure 4. Other medicines were discovered, such as the insulin in the 1920s (Sims et al., 2021).

Figure 4 - Advertisement for Cocaine Toothache Drops in US, 1885 (NIH, 1885)

The table 2 is summarizing a list of apothecaries, their estimated year & country of creation and their relationship with current pharmaceutical companies.

Table 2 - Non exhaustive list of apothecaries with their relationship with current big pharma

Apothecary	Years	Country	Current pharmaceutical company
Merck	1668	Germany	Merck Germany
Hoffmann-La Roche	1896	Switzerland	Roche
Burroughs Wellcome	1880	England	GSK
Midy	1778	France	Sanofi
Etienne Poulenc	1900	France	Sanofi
Abbott	1888	US	Abbott
Smith Kline	1830	US	GlaxoSmithKline
Upjohn	1886	US	Viatris

- *1930 – 60*

This period is identified as the “Golden age” of the pharmaceutical industry (Malerba and Orsenigo, 2015). Alongside with the discovers related to medicine, the field of chemistry saw a growth of development. Synthetic vitamins, sulfonamides, antibiotics, hormones (thyroxine, oxytocin, corticosteroids, and others), psychotropics, antihistamines, and new vaccines were developed at that time.

Table 3 - Example of medicine products discovered between 1930 and 1960

Medicine	Therapeutic area	Year of discovery
Sulfamidochrysoidin	Streptococcal infection	1931
Sulfonamide	Bacterial infection	1935
Equilenin	Sex hormones	1939
Penicillin	Bacterial infection	1939
Cortisone	Anti-inflammatory	1949
Enovid	Contraceptive pill	1956

- *1960 – 80*

During this era, the cost increase of new drugs leads to a change of paradigm and strategies. Alongside with this parameter, the progress in different fields, such as pharmacology, biology, physiology or enzymology, led to a new range of possibilities for drugs development. The birth of the biotechnology is usually identified with the Genentech company in 1976 (Lucier, 2019). But some evidence seems to set Cetus as the first biotechnology company in 1971 (Bains, 2020). Main innovations were brought around cardiovascular drugs; tranquilizers, antidepressants, and antihistamines with fewer side effects; nonsteroidal anti-inflammatory drugs; oral contraceptives; cancer therapies; and means of controlling the symptoms of Parkinson's disease and asthma attacks.

Table 4 - Example of medicine products discovered between 1960 and 1980

Medicine	Therapeutic area	Year of discovery
Ibuprofen	Pain killer	1962
Ketamine	Anesthetics	1962
Triamterene	Blood disorder (pressure)	1964
Amiloride	Blood disorder (pressure)	1967
Diclofenac	Pain killer, anti-inflammatory	1973
Tramadol	Opioid pain killer	1977

- *1980 – present*

As in the past, the increase of knowledge in other scientific fields allowed the pharmaceutical industry to break through new type of medicines. Medicines to treat cancer, such as angiogenesis inhibitors and drugs targeted to molecular features of cancer cells, and to fight HIV/AIDS, such as reverse transcriptase inhibitors and protease inhibitors, were discovered.

Modelization and databases helped to speed up the development process of New Molecular Entity (NME) candidates.

Table 5 - Example of medicine products discovered between 1960 and 1980

Type of medicine	Family type	Therapeutic area	Year of discovery
Sumatriptan	Triptans	Headache	1984
Ketoprofen	Propionic acid	Nonsteroidal anti-inflammatory drugs	1993
Parecoxib	Prodrug of valdecoxib	Anti-inflammatory	1995
Lopinavir	Protease inhibitors	HIV infection	1996
Ropivacaine	Amino amide	Local anesthetic	1998

Dupilumab	Monoclonal antibody	Atopic dermatitis asthma, nasal polyps, eosinophilic esophagitis and prurigo nodularis	2016

A trend seems to appear within the big pharma where "large molecules" are more and more developed. In other words, a switch from the historical chemical-type of medicine and primary care focused, for more profitable specialty care drugs (Gautam and Pan, 2016) is observable.

Moreover, strategies of R&D in the pharmaceutical industry are changing, in order to inverse the decline of NME discovery. Schuhmacher et al. mentioned the *"outsourcing of non-core activities", the "externalization of research activities to biotech companies"* who are more agile, the *"open innovation"*, the *"vitualization of R&D"*, or *"public-private partnerships"* as approaches that the pharmaceutical industry is currently adopting (Schuhmacher et al., 2021).

The pharmaceutical industry, a societal actor

Intrinsically part of its Societal duty, the Pharmaceutical sector is one of the key actors to ensure the availability (Gateaux and Heitz, 2008) and the affordability (Nussbaum, 2009) of treatments. It is therefore one of the key players to contribute to the Sustainable Development Goal (SDG) number 3 *"Ensure healthy lives and promote well-being for all at all ages".* But like any Human activity, the manufacture of medicine products induces environmental impacts. Therefore, the Pharmaceutical sector is facing the ethic complexity to provide efficient healthcare product by non-degrading the environment (Luu et al., 2021).

Even if Environmental issues are more and more visible and considered as critical within the International community, especially the Climate change (IPCC, 2021), few examples shows that we are currently still in an Anthropocentric mindset. It is particularly explicit within the pharmaceutical sector. For instance, a declaration of the European Medicines Agency (EMA) mention that *"In any event this [potential environmental] impact should not constitute a criterion for refusal of a marketing authorisation"* (EMA, 2006). A concrete example of this statement is the case of the COVID-19 vaccines. Despite the complex cold supply chain, and by extension a high energy consumption, the deployment of such products was adapted to face the pandemic crisis. The Carbon emissions equivalent of the vaccines were evaluated around 5.13×10^{12} gCO_2eq for 1.56×10^{10} vaccine doses (Klemeš et al., 2021). To illustrate a bit more, if we consider the distance by roads between Paris and Dakar at 6,882 km (Himmera, 2021) and based on the Environmental Protection Agency (EPA) calculation tool (OAR US EPA, 2015), the Carbon emissions equivalent of the vaccines may represent around 3 million Paris-Dakar in an average vehicle.

Another environmental concern, specific to the pharmaceutical products, can be mentioned. The eco-toxicity is one of the critical issues of the pharmaceutical sector. The chapter II.5.4 is describing this aspect.

A group of Pharmaceutical associations joined themselves to publish during the UN Climate Change conference COP26 a joint statement who declare that member of those associations are mitigating the Environmental impact of their activities who are contribution to climate change (ABPI et al., 2021). As example of the change of paradigm from stakeholders of the pharmaceutical industry, in France, the Union of Hospitals for Purchasing (UniHA) had organized a webconference to talk about how to limit the environmental footprint of hospitals, from a market point of view (UniHA, 2021).

I.3 Scientific context

Environmental dimension

From a scientific point of view, the Planetary boundaries are setting a framework of "nine processes that regulate the stability and resilience of the Earth system" (Rockström et al., 2009). A recent update proposed a quantification of the Novel entities (NE) boundary which was performed

not so far (Persson et al., 2022). Like any Human activity, the pharmaceutical industry is a contributor in the degradation of each Planetary boundary.

Challenges mentioned previously are part of multiples areas of expertise, which goes from the fields of Environment sciences, Formal sciences, to the Human and Social ones. The work presented is this manuscript is included in the research field of Eco-design, as defined by the international community (ISO, 2020). It is at the interface between the Engineering design and the Environmental sciences.

Design science and engineering

Ralph & Wand identified 33 definitions of "design". They proposed a list of 19 concepts linked to those definitions. Main ones are considering "design" as: "process"; "creation"; "planning"; "physical activity"; "system"; "being deliberate or having a purpose, goal or objective"; "activity" or "occurring in an environment" (Ralph and Wand, 2009).

In Design Research Methodology, Blessing & Chakrabarti states that "design" include:

"Activities that generate and develop a product from a need, product idea or technology to the full documentation needed to realize the product and to fulfil the perceived needs of the user and other stakeholders. The perceived need may be social (e.g., transportation means) as much as economic (e.g., manufacturing systems for mass production). The impulse to start such a process can come from: the market, such as needs of customers and competing products; internal needs of product development enterprises, such as new developments, cost reduction, production automation and diversification goals; and from other sources, such as research results, legislation, environment, society and politics" (Blessing and Chakrabarti, 2009).

Within engineering sciences, the field of "design" covers the theories, methodologies, methods, and tools guiding the practice of design. Its purpose is to guide designers in their steps by formalizing approaches allowing them on the one hand to correctly apprehend a problem, and on the other hand to solve it. Four main areas can be distinguished within the engineering sciences of design (Hubka and Eder, 1982):

Table 6 - The four main areas of the engineering sciences of design, based on Hubka (Hubka and Eder, 1982)

Area	Description
Theory of technical systems	Focuses on understanding artifacts (artificial systems) by modeling their mechanical properties, their structure, their operation, their cost, their social context, etc. This domain contains all "knowledge about the object targeted by the design process"
Theory of the design process	Focuses on the action of the designer. It brings together a set of processes, methods and technical tools used by the designer. This domain contains the formalization of the designer's knowledge and know-how.
Theories from the human and social sciences	Focuses on the functioning of design teams and more particularly on the generation and transfer of information, and therefore of knowledge, in all its forms.
Design methodologies	Focuses on design methods with the aim of leaving design by intuition and entering structured design. Models to guide the designer at each stage of the design process are explored. Research in this field aims to consider new factors making it possible to anticipate parameters such as risk, quality, etc. as far upstream as possible

Within this context, our work is positioned at the intersection between theory of technical systems (environmental impact modelization), theory of the design process (adaptation of tools and processes), theories from the human sciences (communication and transfer of information within interdisciplinary teams), and theory of the design methodologies (practice of eco-design).

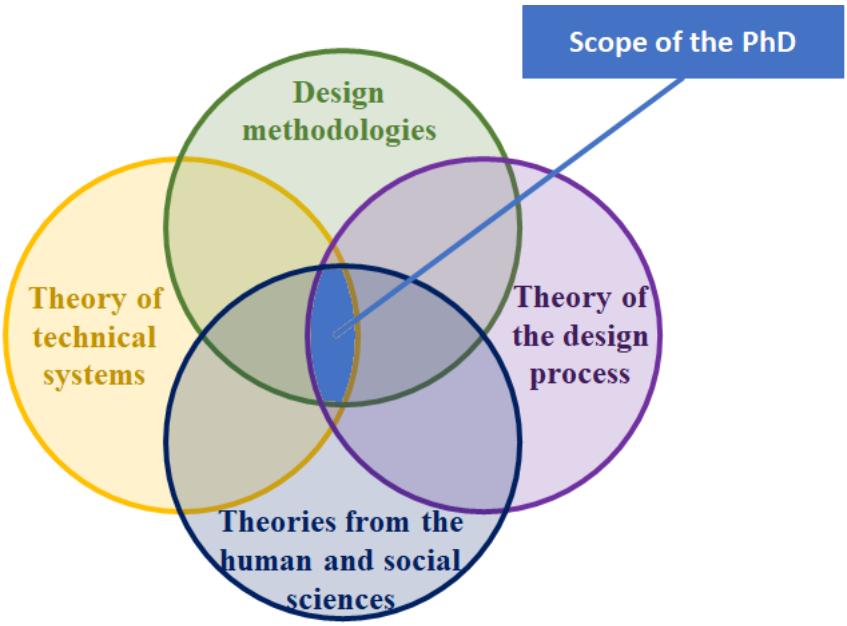


Figure 5 - Scope of the PhD within the design science framework of Hubka

Design for Sustainability

To comprehend the Design for Sustainability, we first need to understand what is behind the terminology of "sustainability" as the term "design" in science and engineering was described above.

Sustainability

The concept of sustainability can be defined as the intersection of the three dimensions: environmental, social, and economic performance, as described by the triple bottom line (Elkington, 1998).

In the literature review of Arena et al., the authors highlighted that the academic perspective of the sustainability is including several sub-dimensions, within each dimension, as shown in the table 7 (Arena et al., 2009).

Table 7 - Sub-dimensions of the sustainability, adapted from (Arena et al., 2009).

Dimension	Environmental	Social	Economic
Sub-dimension	• Materials • Energy • Water • Biodiversity • Emissions • Waste • Product and services	• Work practices and adequate working conditions • Diversity and equal opportunities • Relations with the community • Social policy compliance • Consumer health and safety • Human rights	• Economic performance • Market presence • Indirect economic impacts

Design for Sustainability

Rocha et al. are defining the Design for Sustainability (DfS) as *"a holistic design approach that enables to integrate and assess the sustainability dimensions in different stages of the product or product-service development process towards the required scale of incremental and/or radical innovations"* (Rocha et al., 2019).

The field of DfS appeared in the first half of the 1990s from the integration of environmental aspects in a material and component centric approach, to a more global one with socio-technical system perspective (Ceschin and Gaziulusoy, 2019). Alongside with those two levels, Procut level, Product-Service System level and the Spatio-Social level are defining the overall framework of DfS. Several approaches exist today to work on these different levels.

Eco-design

The eco-design is a concept part of the DfS. In this part, we aim to expose several definitions, set the one used in this manuscript and propose a quick history of the approach.

Definition

The concept of "eco-design" is defined by the ISO 14006:2020 norm as below (ISO, 2020):

"Systematic approach that considers environmental aspects in design and development with the aim to reduce adverse environmental impacts throughout the life cycle of a product"

The definition from the European commission is quite similar (European Commission, 2009):

"Ecodesign" means the integration of environmental aspects into product design with the aim of improving the environmental performance of the product throughout its whole life cycle

In the United States, the Environmental Protection Agency do not use the term "eco-design" but "green engineering". The concept present similarity with "eco-design" and is defined as (OCSPP US EPA, 2015):

"Green engineering is the design, commercialization, and use of processes and products in a way that reduces pollution, promotes sustainability, and minimizes risk to human health and the environment without sacrificing economic viability and efficiency.

Green engineering embraces the concept that decisions to protect human health and the environment can have the greatest impact and cost-effectiveness when applied early, in the design and development phase of a process or product."

In the scientific literature, several authors are defining "eco-design" with the integration of environmental aspects into the design process. Table 8 presents a non-exhaustive list of them.

Table 8 - Definition of eco-design in the scientific literature with the environmental aspect

Definition	Reference
"Design which addresses all environmental impacts of a product throughout the complete life cycle of the product, without unduly compromising other criteria like function, quality, cost and appearance"	(Dewberry and Goggin, 1995)
"EcoDesign focuses on the integration of environmental considerations in product development"	(Karlsson and Luttropp, 2006)
"Lowering environmental impact focusing on the whole life-cycle of products from extraction of raw materials to final disposal"	(Ceschin and Gaziulusoy, 2016)
"Ecodesign is an approach to include environmental requirements into the product development process"	(Schäfer and Löwer, 2021)

More recently, authors included in the concept of "eco-design" the broader aspect of Sustainability. Table 9 presents a non-exhaustive list of them.

Table 9 - Definition of eco-design in the scientific literature with the sustainability aspect

Definition	Reference
"Development of new and more environmental-friendly products that have the potential to result in innovative solutions with an enhanced sustainability performance"	(Maccioni et al., 2019)
"Eco-design is used as a tool in the product and service sectors with the aim to increase sustainability and reduce negative environmental impact on the product design stage"	(Varžinskas et al., 2020)
"The concept of eco-design is a strategies system that goal for balancing and integrating of economic, environmental, and social aspects during its whole life cycle in product design phase"	(Mohammed et al., 2021)

In this manuscript, the author is defining "eco-design" as:

"Integration of the holistic environmental aspects into product or service design with the aim of improving the environmental performance of the product throughout its whole life cycle; without unduly compromising other criteria like function, quality, cost and safety"

I.4 Research laboratory context

The Product Design and Innovation Laboratory (Laboratoire Conception de Produits et Innovation, LCPI, EA 3927) is a research laboratory of Arts et Métiers Institute of Technology, who is working in the field of Industrial Engineering. It was founded in 1978 by the Professor Robert Duchamp. The three missions of LCPI (Teaching, Research and Industrial Valorization) are closely integrated and feed a single and unifying theme: the optimization of the Design and Innovation Process. The research activities benefit from both of academic roots and the industry. The LCPI team is multidisciplinary, like the stakeholders involved during the design process: its composition draws mainly on the Engineering Sciences, and the Human & Social Sciences.

- *Laboratory position*

The LCPI is structured around two themes of Research. The Design engineering for the first one, and the Management & Support systems as the second. From those two, axes from skills perspective and processes ones are defined. Finally, six platforms of competences are formalized in order to support the overall activity of the laboratory, as shown in the figure below.

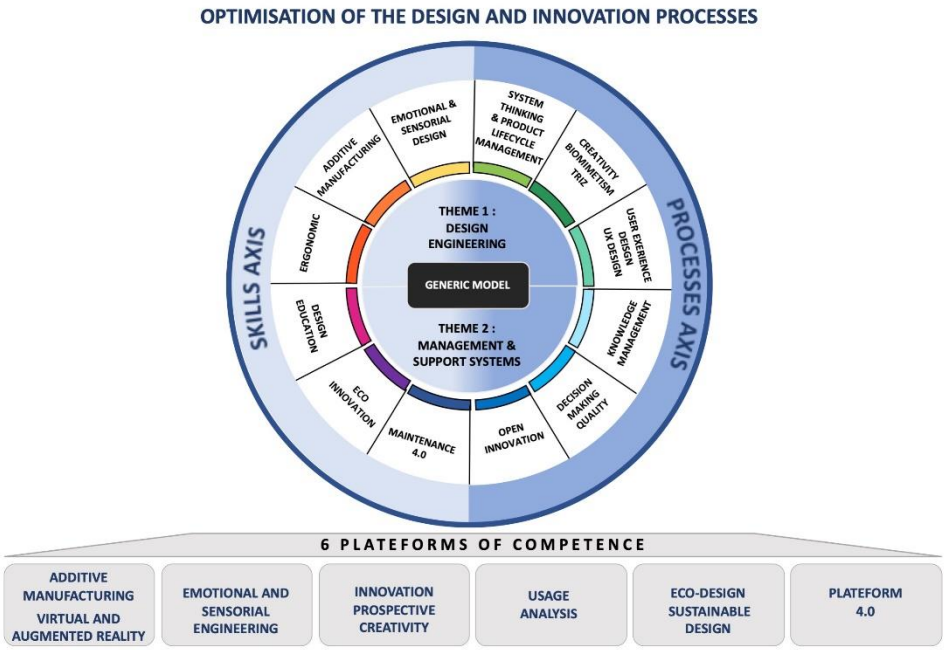


Figure 6 - Overall Research positions of the LCPI

This PhD is related to the "Eco-innovation", "Knowledge management" and "Product Lifecycle management" axis of the laboratory, alongside with the "Eco-design Sustainable design" platform of competence.

- *LCPI legacy*

Research in the field of "Eco innovation" can be found since 2000 in the digital archive of the LCPI, with the work of Marc JANIN (Janin, 2000). Since then, 22 studies related to this skill axe were performed, including the one described in this manuscript. The "Knowledge management" is also a topic well explored with around 22 PhDs with a topic related to this process axe. Last axe relevant to this manuscript, the "System thinking & Product Lifecycle management" is fed with 46 PhDs since 2000.

The work described in this manuscript came these previous studies performed by other researchers of the laboratory. The figure 7 is presenting a framework of some of them and the appendix 1 present all the PhDs that can be found in the digital archives.

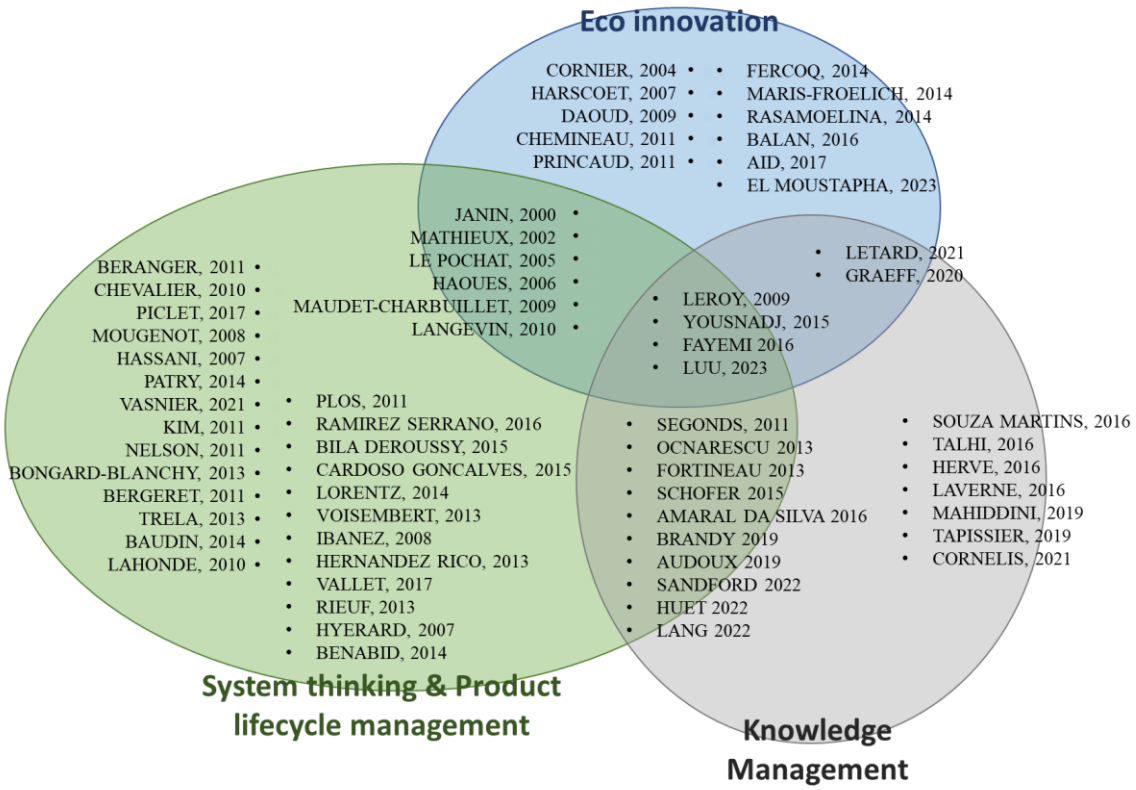


Figure 7 - Framework of the PhDs performed in the LCPI with the same skills & processes axis of the research in this manuscript

The LCPI had various collaboration with the health-care sector, and three of PhDs were focused on medical devices plus one specifically on drug acceptability.

I.5 Stakes of the work

Through the different prisms contextualizing our work, it is possible to highlight three main dimensions of this work.

- *Societal dimension, the environmental crisis*

The Humankind is facing a global environmental crisis. The changes of ecosystems will lead to the modifications of the way of living and the place of the Human being inside the environmental whole.

The stake of this work is to contribute to foster innovation with the holistic vision of environment, with the aim to minimize the environmental burden of the Human activity.

- *Scientific dimension, understand the levers of the pharmaceutical sector*

Approaches to integrate the environment into design practices is not a new topic. However, levers to improve the environmental footprint of the pharmaceutical sector is still a topic to explore.

The stake of this work is to contribute to the identification of the environmental levers of the pharmaceutical sector.

- *Industrial dimension, the integration of Eco-design practices within the pharmaceutical sector*

The pharmaceutical sector has the intrinsic duty to make available treatment for population to ensure the well-being of the Humankind. However, the environmental footprint of their products is

not neutral. By extension, those products may damage the environment, making at risk future populations. Therefore, an ethical question can be raised “should we treat the current population and put in the danger the future generation?”. To avoid this eternal and endless debate, the pharmaceutical sector needs to ensure a proper development of its products. The integration of Eco-design into its practices appear key.

The stake of this work is to contribute to foster Eco-design in a systemic manner within the pharmaceutical sector, with the aim to minimize the environmental burden of its activity.

I.6 Summary of the work context

Through the presentation of the context linked to this doctoral thesis, the general framework of this work is established.

This framework relies on scientific, academic, industrial, and societal criteria, criteria that will guide the structuring of the reasoning formalized throughout this thesis. It also represents both a continuity and a novelty of the research performed by the LCPI. A continuity with the legacy of the previous works regarding “Eco-innovation”, “Knowledge management” and “Product Lifecycle management” and the research in the health-care sector. It is also a novelty with the merge of the knowledge of the laboratory regarding these research axes and the health-care industry, by integrating the environmental perspective into the development of medicine products, which were not only not explored in the laboratory but is also an emergent topic in the pharmaceutical sector.

In the next chapter, the state of the art will be presented in order to establish the scientific foundations of the research presented in this manuscript. This will then lead to the formulation of a problem and hypothesis, who aims to feed the stakes formalized previously.

Phase 1

Chapter II

State of the art

« Diagnostiquer, c'est littéralement « voir à travers » (dia gnosis), établir une connaissance qui dépasse celle du sens commun, créer une lucidité nouvelle sur la réalité quotidienne. »
Françoise PIOTET, Renaud SAINSAULIEU, « Méthodes pour une sociologie de l'entreprise », 1994

"To diagnose is literally to "see through" (dia gnosis), to establish a knowledge that goes beyond that of common sense, to create a new lucidity on daily reality."
Françoise PIOTET, Renaud SAINSAULIEU, « Méthodes pour une sociologie de l'entreprise », 1994

II State of the art

All state of the art begins with a literature review. The literature review can be defined as a process to *"identify the theories and previous research which have influenced* [the] *choice of research topic and the methodology to adopt"* (Ridley, 2008). This chapter aims to describe these elements, in order to have a diagnosis and identify the approach of this thesis.

II.1 Structure of the state of the art

As described briefly previously, this work is a legacy of different fields. The heart of this thesis is around the Eco-design within the pharmaceutical industry. The position of the work suggested in the chapter one invite us to have a look on different scientific fields.

The design science and engineering are one of the entry points of the thesis (chapter II.2). The description of the main associated frameworks, theories, and processes appear as the first key of scientific understanding for a formalization of an Eco-design approach within the pharmaceutical sector.

Secondly, the Design for Sustainability (chapter II.3) is introduced with the aim to explicit the main concepts. As a main topic of this research, a dedicated focus on Eco-design is proposed.

Afterwards, consideration regarding medicine products is proposed (chapter II.4). Specificities of such products are mentioned. Finally, current links between medicine products and environment are explained (chapter II.5), from a lifecycle perspective and the actual environmental approaches within the pharmaceutical sector.

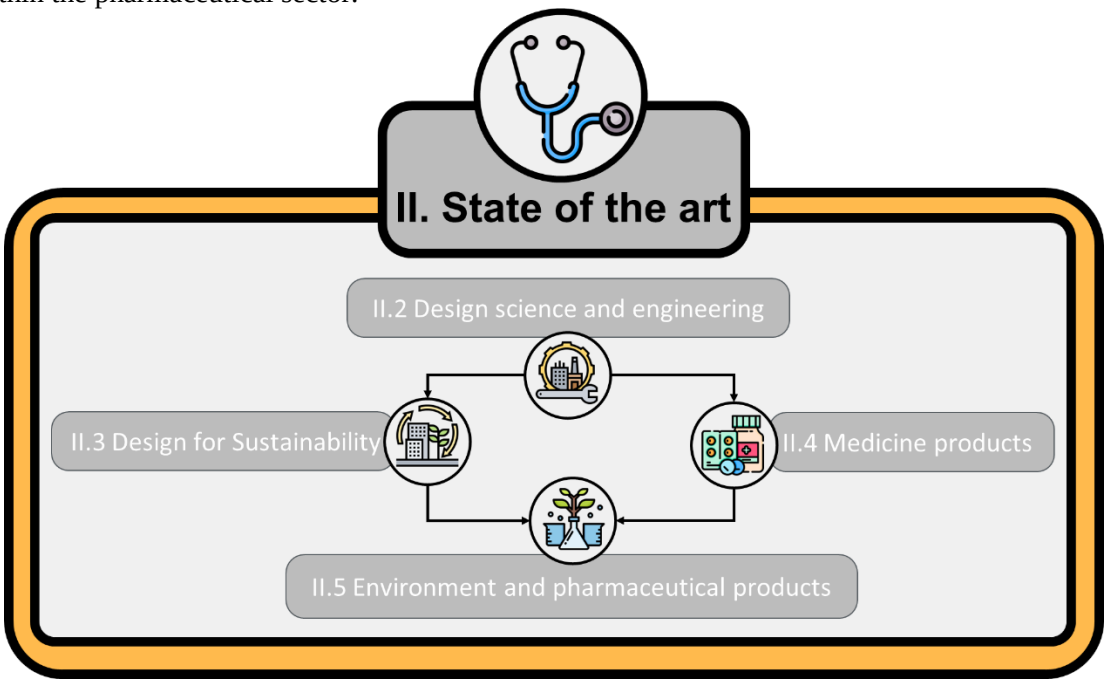


Figure 8 - State of the art chapter structure

II.2 Design science and engineering

The purpose of this part is not to present an exhaustive list of product design methodologies. The literature abounds of reviews that describe different practices (Schmidt et al., 2009), key of success (Cooper, 2019) and even tool to choose the right methodology (Lahonde et al., 2010). The aim of this part is to reflect the diversity of methodologies related to the plurality of needs.

- *Systematic Design*

As described by Lahonde, Pahl and Beitz influenced many designers with their methodology, based from the German design science (Lahonde, 2010). They structured their method around four

phases, Clarification of the task, Conceptual design, Embodiment design, and Detailed design. Those includes several steps as shown in the figure below.

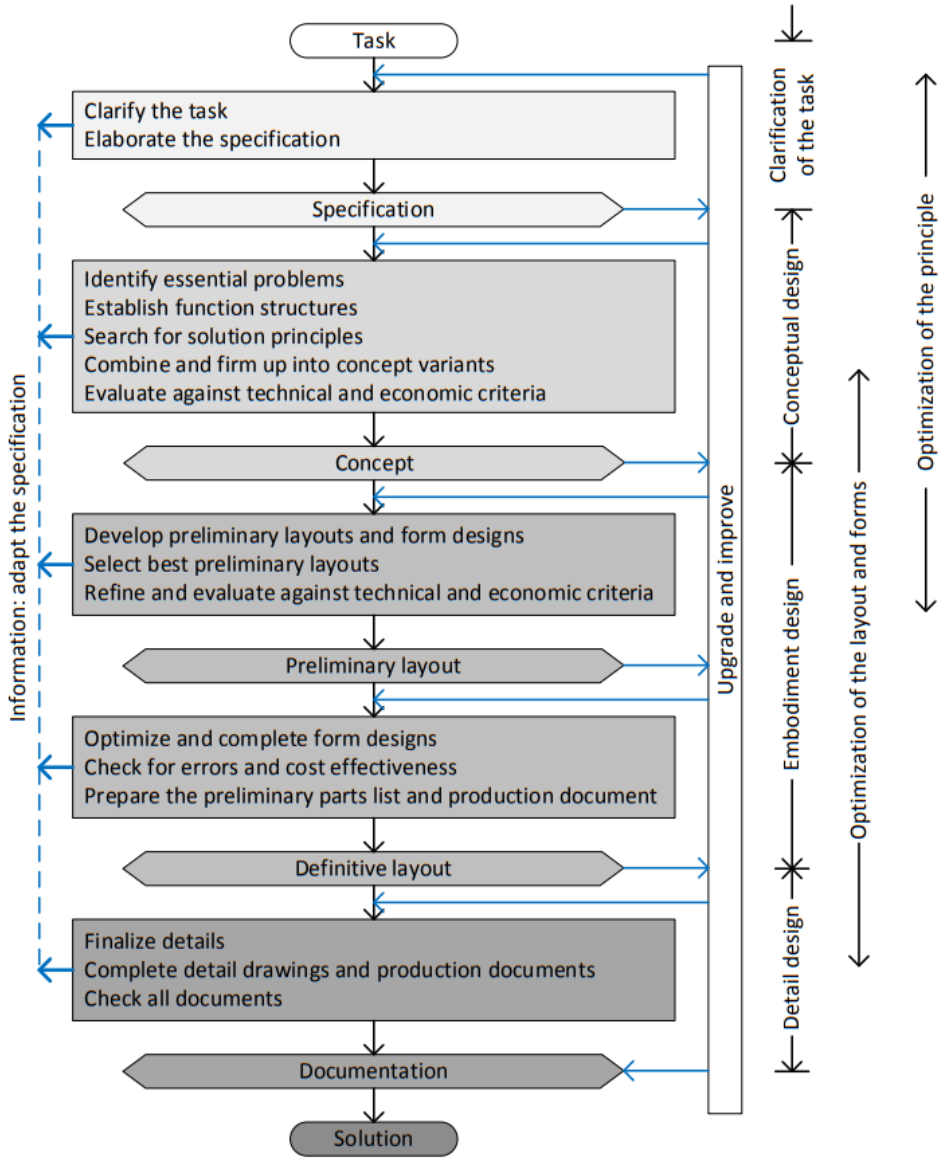


Figure 9 - Systemic design approach, from Lahonde (2010)

- *Axiomatic Design*

Developed by the Professor Suh Nam Pyo (Suh, 1990), the Axiomatic design is a methodology based on 4 principles who aims to systemize the assessment of the user needs & design parameters to translate them, respectively, in functional requirements & process variable.

Table 10 - The four principles of the Axiomatic Design

Principle	Description
1st: Domains	Definition of 4 domains: • Customer: customer needs • Functional: define Functional Requirements • Design: define Design Parameters • Process: define Process Variable
2nd: Hierarchies	From a FR, a DP is defined. From this Design Parameters, some sub Functional Requirements are defined and so on

3rd: Zigzag	Iterative process between all domains
4th: Axioms	1. Independence: Functions (constraints and principal) must be independent of each other 2. Information: Minimize system complexity and product design information

- *TRIZ*

Basically, TRIZ is a Russian methodology to solve problems. It was developed by Genrich Saoulovitch Altshuller (Cavallucci, 2016). It is a systematic approach for finding solutions to technical problems (Ilevbare et al., 2013).

The approach consists in a four steps process as describe in the figure below.

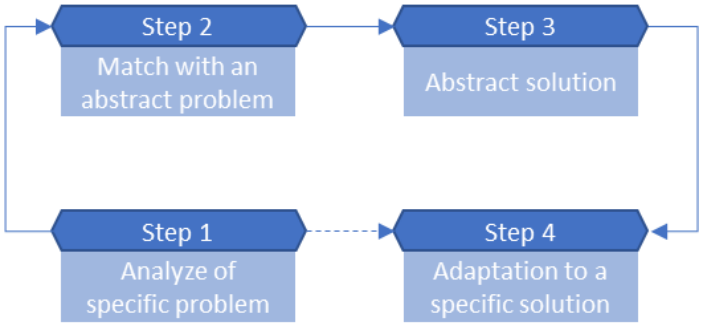


Figure 10 - The four steps of the TRIZ methodology, adapted from Moehrle (Moehrle, 2005)

The literature shows some positive sides of TRIZ (Ilevbare et al., 2013). such as the approach to problems, the volume of idea generation, the rapidity and the teamworking approach.

Some limits were also identified (Ilevbare et al., 2013)., like the rigidity and lack of agility of the method, the difficulty in acquisition and application of TRIZ knowledge, the cultural issues, organizational and the lack of standard

- *C-K theory*

The C-K theory is a design approach using two interdependent spaces between Concepts (C) and knowledge (K) (Hatchuel and Weil, 2009). Hatchuel defined his methodology as follows (Hatchuel and Weil, 2003):

"assuming a space of concepts C and a space of knowledge K, we define Design as the process by which a concept generates other concepts or is transformed into knowledge, i.e. propositions in K."

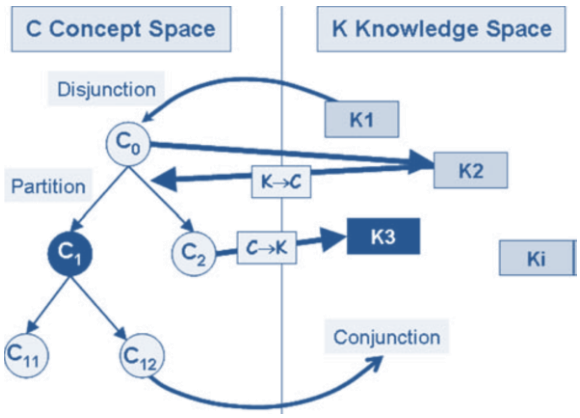


Figure 11 - Asymmetric structure of spaces C and K from Hatchuel, (Hatchuel and Weil, 2009)

- *New Product Design*

The New Product Design is an approach of the Professor Aoussat. It is a holistic methodology of design, based on four stages (Aoussat et al., 2000).

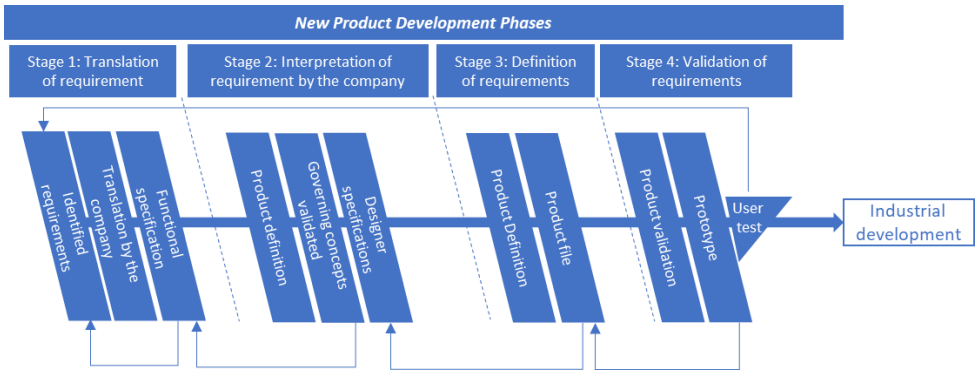


Figure 12 - New Product Design methodology, adapted from Aoussat

- *Stage gate ® & Agile Stage Gate ®*

The Stage Gate® is a holistic methodology set by Cooper who split the development of product into 6 stages and 5-gates. The stages are similar to the New Product Design previously presented. It includes the Idea generation, the Idea scoping, the Business case, the Development, the Tests & Validation and finally the Launch of product (Vedsmand et al., 2016).

The Agile Stage Gate® associate the Agile project management into the previous approach (Vedsmand et al., 2016). The main purpose of it is to increase the performance results by providing a framework to work with uncertainties and by more interaction between project team and both users & consumers.

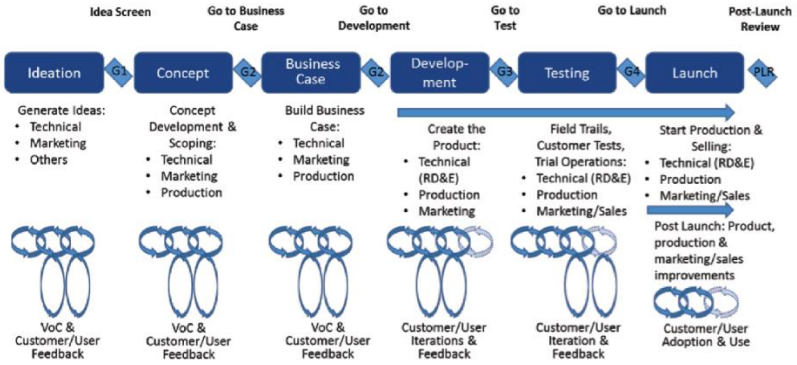


Figure 13 - The integrated Agile-stage-gate hybrid model – a typical 6-stage 5-gate Stage-gate idea-to launch system, with Agile built into each of the stages (Cooper, 2018)

- *Generic stages of a product's life cycle*

As mentioned by Jamnia even if no standard definition can fit all process, she proposed a simplistic product life cycle with generalized steps (Jamnia and Atua, 2019). She described this process in three phases, the New Product Development (NPD) Phase, the Product Sustaining Phase, and the End of Life Phase.

Even if the business case and concept selection are not in the same order, we can find similarities between the NPD proposed here, the one of Aoussat and with the Stage Gate®.

This framework put the launch and industrialization as the Sustaining step of the product, where the product reaches its maturity and stability. The last piece describes the step of the life cycle where the product is no longer profitable.

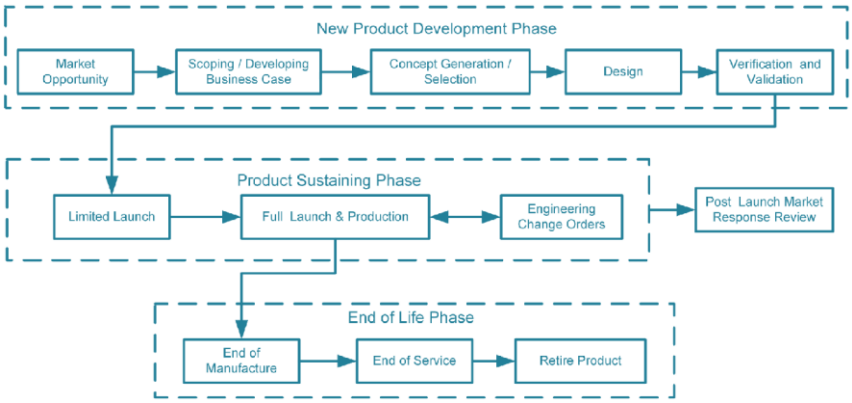


Figure 14 - Typical stages of a product's life cycle from Jamnia 2019 (Jamnia and Atua, 2019)

- *Summary*

With the different example of methodologies, we can understand that some methodologies are focused on specific problems, such as TRIZ & C-K and some of them have a more holistic approach in terms of life cycle of the product. The table 11 tries to summarize a non-exhaustive list of aspects of the methodologies seen above.

Table 11 - Non exhaustive list of Design methodology with their target, some advantages and limits

Methodology	Target	Advantages	Limits
Systemic design (Pahl et al., 2007)	Holistic approach	Can apply to most of products	Lack of specificities
Axiomatic design (Felicia Veronica and Draghici, 2003)	Focus on user needs	Idea generation Reduce random search process	Application difficulty Require knowledge
TRIZ (Ilevbare et al., 2013)	Problem resolution	Idea generation Rapidity Teamworking	Lack of standard Application difficulty Rigidity
C-K theory (Choulier et al., 2011)	Problem resolution	Map Concept & Knowledge Practical	Restricted theory
New Product Design (Shepherd and Ahmed, 2000)	Holistic approach	Transversal approach Reduce development cost Better time to market	Bureaucratic Tighter controls Cross functional changes
Agile Stage Gate ® (Cooper, 2018)	Holistic approach	Flexibility Productivity Team coordination	Resource allocation Proliferation of meetings Bureaucratic
Generic stages of a product's life cycle (Jamnia and Atua, 2019)	Holistic approach	Can apply to most of products	Lack of specificities

II.3 Design for Sustainability

II.3.1 Overall framework

The field of Design for Sustainability (DfS) emerged in the 90's with a focus on environmental aspects of individual products, through the Green design approach (Burall and Council, 1991; Mackenzie et al., 1997). DfS approaches evolved within the years to broader the environmental, social, and economical perspectives. These approaches can be defined in different levels as defined by Ceschin (Ceschin and Gaziulusoy, 2019). The figure below presents a framework of the approaches of DfS within the different levels.

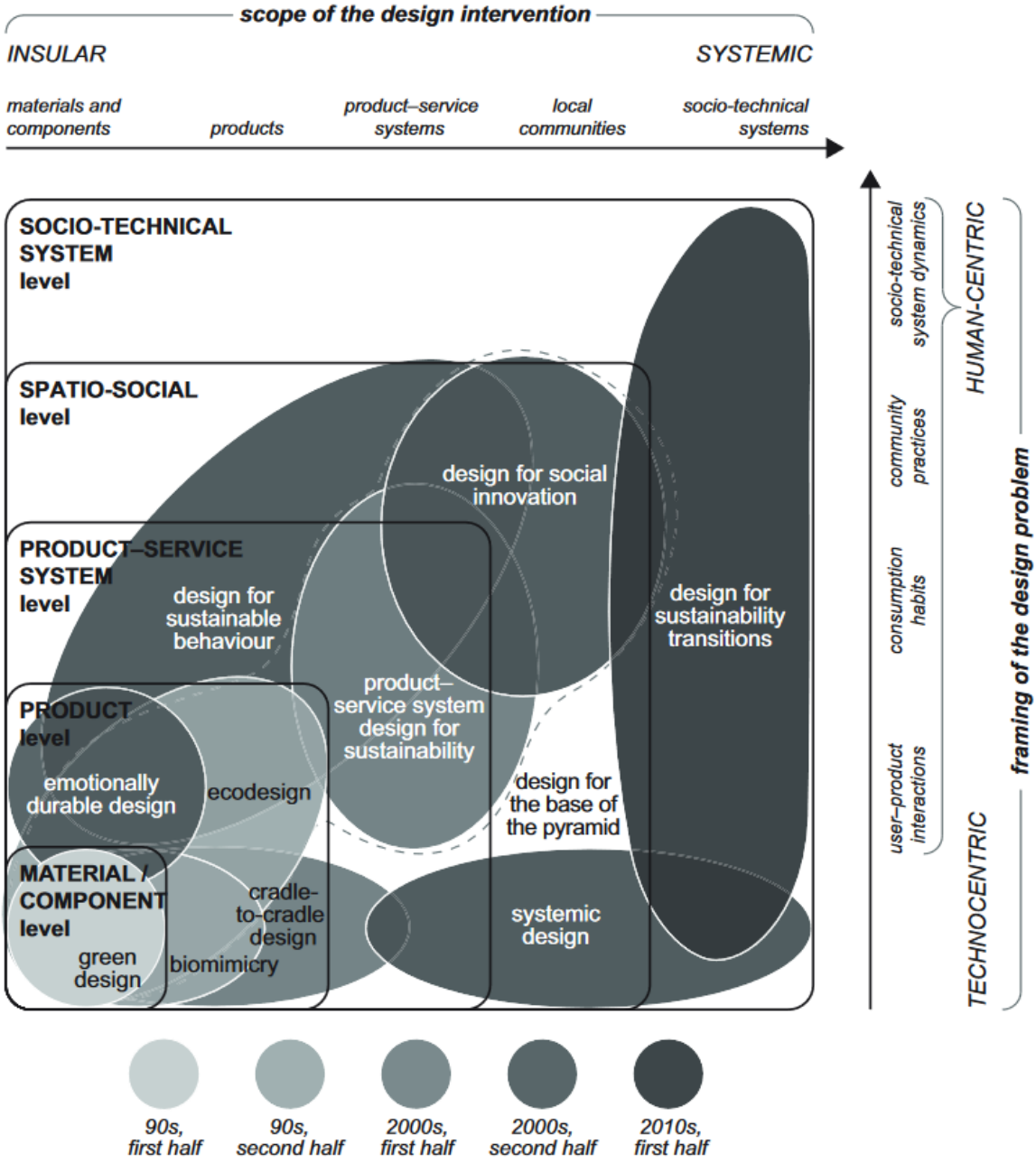


Figure 15 - Evolution of the DfS field, from Ceschin (Ceschin and Gaziulusoy, 2019)

Table 12 presents a definition of the DfS approaches, with their related sustainability dimensions.

Table 12 - DfS approaches definitions with their Sustainability dimensions

Approach	Description	Sustainability dimension	Reference
Green design	*Lowering environmental impact through redesigning individual qualities of individual products*	Environmental Economic	(Ceschin and Gaziulusoy, 2016; Dowie, 1994)
Emotionally durable design	*Strengthening and extending in time the emotional attachment between the user and the product*	Environmental Economic	(Ceschin and Gaziulusoy, 2016; Chapman, 2005)
Eco-design	*Lowering environmental impact focusing on the whole life-cycle of products from extraction of raw materials to final disposal*	Environmental Economic	(Ceschin and Gaziulusoy, 2016; Schäfer and Löwer, 2021)
Cradle-to-cradle design	*Emphasis on a regenerative approach by the industry and closing the loops; focus on non-human species and future generations*	Environmental Economic	(Braungart and McDonough, 2009; Ceschin and Gaziulusoy, 2016)
Biomimicry	*- Mimicking nature in design of forms, products and systems by using nature as model, measure and mentor.* *- Learning from living beings in order to design in a more sustainable way*	Environmental Economic	(Ceschin and Gaziulusoy, 2016; Fayemi et al., 2017; Graeff, 2020)
Design for sustainable behaviour	*Making people to adopt a desired sustainable behaviour and abandon an unwanted unsustainable behaviour*	Environmental Social Economic	(Ceschin and Gaziulusoy, 2016; De Medeiros et al., 2018)
Product-service system design for sustainability	*Go to the root of the sustainability problem by delivering functions instead of products or services with a focus on both environmental and economic dimensions*	Environmental Social Economic	(Ceschin and Gaziulusoy, 2016)
Design for social innovation	*Innovations aiming to solve social problems such as poverty, access to safe drinking water or those targeting behavioral change and social well-being*	Environmental Social Economic	(Ceschin and Gaziulusoy, 2016)
Design for the base of the pyramid	*Improving the lives of people who live at the base of the pyramid through market-based solutions through 12 principles*	Environmental Social Economic	(Boradkar and Kulkarni, 2010; Ceschin and Gaziulusoy, 2016)
Systemic design	*Implement sustainable productive systems in which material and energy flows are designed so that waste from one productive process becomes inputs to other processes.* *Prevent waste from being released into the environment.* *Result in new, locally-based, value chains.*	Environmental Economic	(Ceschin and Gaziulusoy, 2016)

Design for sustainability transitions	*Transform socio-technical systems through technological, social, organizational and institutional innovations*	Environmental Social Economic	(Ceschin and Gaziulusoy, 2016)

Despite the plurality of methods, Sherwin described a lack of implementation of DfS practices within the development of products and services in industry (Sherwin, 2004). This observation was reinforced by Faludi et al., where the authors defined a roadmap to foster the integration of Sustainability within the design research community (Faludi et al., 2020). They proposed short-, medium-, and long-term tasks, for both academics and industries. The figure below highlights the contribution to foster the integration of Sustainability within the industry.

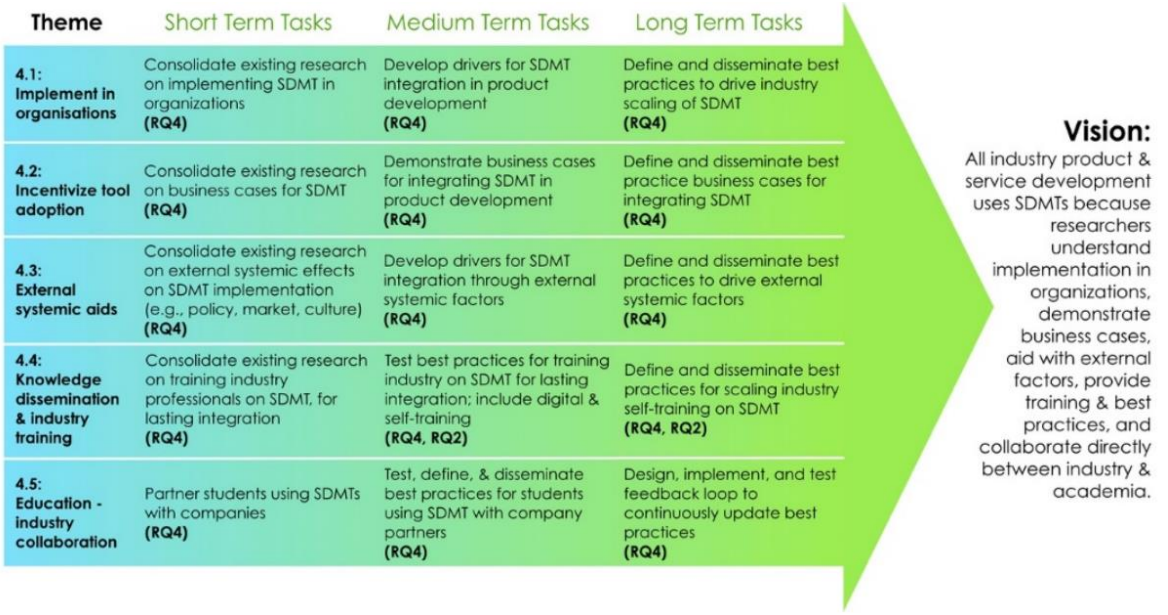


Figure 16 - Short-, medium-, long-term tasks identified to foster the Sustainability within the industry, from Faludi (Faludi et al., 2020)

II.3.2 Eco-design

As mentioned in the table 12, Eco-design can be defined as below:

"Lowering environmental impact focusing on the whole life-cycle of products from extraction of raw materials to final disposal" (Schäfer and Löwer, 2021).

A similar definition is proposed by the ISO norm 14006: *"integration of environmental aspects into product design and development, with the aim of reducing adverse environmental impacts throughout a product's life cycle"* (ISO, 2020)

The European commission defines Eco-design as: *"The integration of environmental aspects into the product development process, by balancing ecological and economic requirements. Eco-design considers environmental aspects at all stages of the product development process, striving for products which make the lowest possible environmental impact throughout the product life cycle."* (EEA, 2001). They have published on 30 March 2022 a proposal for a new Ecodesign for Sustainable Products Regulation (European Commission, 2022). In this proposal, a framework is proposed to structure a range of requirements which include the aspects stated below:

- product durability, reliability, reusability, upgradability, reparability, ease of maintenance and refurbishment.
- restrictions on the presence of substances that inhibit the circularity of products and materials.
- energy use or energy efficiency of products.
- resource use or resource efficiency of products.
- minimum recycled content in products.
- ease of disassembly, remanufacturing and recycling of products and materials.
- life-cycle environmental impact of products, including their carbon and environmental footprints.
- preventing and reducing waste, including packaging waste.

But this recent element is one step of a long journey who started decades ago. Trace of first Eco-design mindset can be found around 1971 (Papanek, 1971). In their review, Schäfer and Löwer showed that the Eco-design topic was formalized within the scientific community in the 90's (Schäfer and Löwer, 2021).

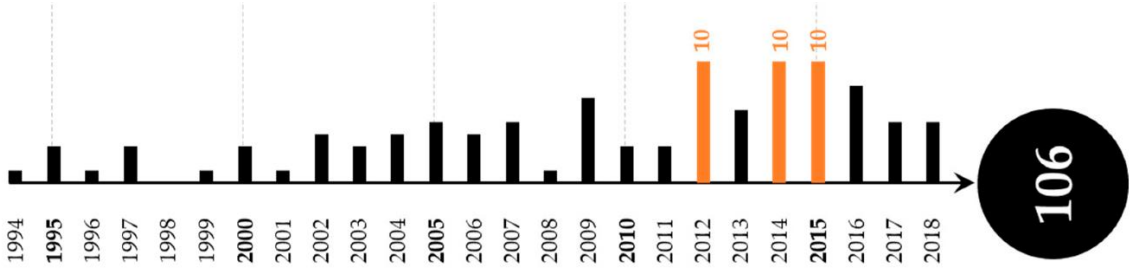


Figure 17 - Number and publication year of references that were retrieved and analyzed in the review of Schäfer and Löwer (Schäfer and Löwer, 2021)

By typing "Eco-design" in the research bar of Google Scholar, it is possible to see 15 900 items from 2019 and 2023, showing the interest of this field nowadays.

- *Eco-design integration framework*

Brones and Monteira de Carvalho assessed 52 models to integrate Eco-design, with a first framework established in 1993 (Brones and Monteiro de Carvalho, 2015). They formalized a harmonized model to foster the integration of Eco-design practices with two dimensions of integration with one sub-divided in three levels, as shown in the figure 18.

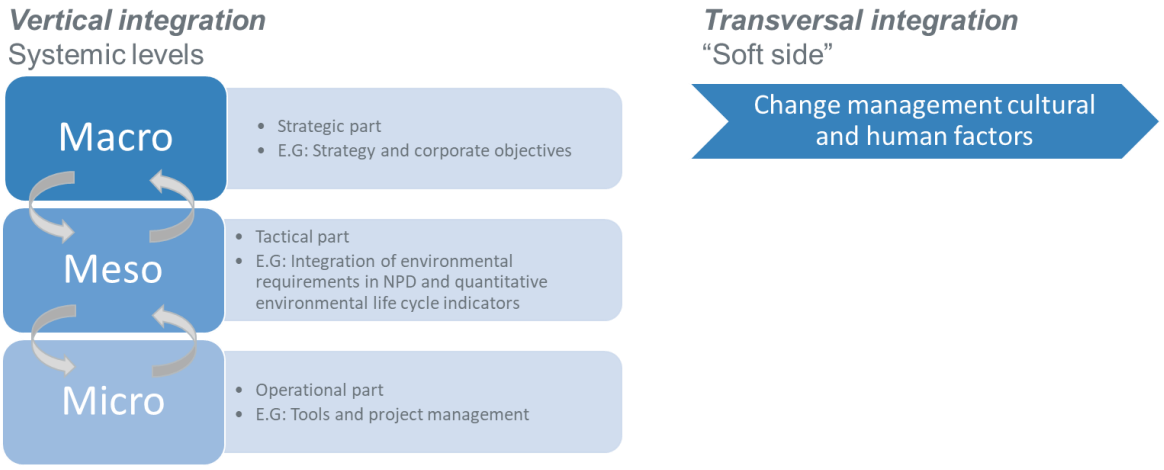


Figure 18 - Eco-design integration model of Brones and Monteira de Carvalho (Brones and Monteiro de Carvalho, 2015)

In this model, the levels of the vertical integration have interconnections and are defined as below.

Vertical integration

- **Macro level:** this level is related to the strategy and global objectives. For a company, it means that they should have quantified environmental sustainability targets with a temporality (e.g.: all new products are Eco-designed by 2030). Those objectives allow to diffuse Eco-design internally within business units and activities. These objectives can also be promoted to external stakeholders (e.g.: shareholders, payers, deciders, users).
- **Meso level:** this level is related to the integration of environmental requirement into the development process of products or services. Companies should have identified key milestones in the development process which are relevant in the decision making and set of the environmental footprint.
- **Micro level:** this level is related to the tools used by teams who support the development of products or services. They aim to guide the decision making by providing either quantitative or semi-quantitative figures, and qualitative approaches. This piece will be developed later in this part.

The **transversal integration** is related to the "Soft side", in other words, the change management such as the cultural changes & the human factors. The field of change management abounds of literature (Al-Ali et al., 2017; Belias and Koustelios, 2014; Eti-Tofinga et al., 2018; Kavanagh and Ashkanasy, 2006) and is not in the scope of the manuscript. Some literature review can be noted (Jayatilleke and Lai, 2018; Stouten et al., 2018), and the integration of sustainability in the field of change management seems to be explored (Universidad Rey Juan Carlos et al., 2021; Verhulst et al., 2007).

- *Eco-design tools*

The literature abounds of Eco-design tools and literature review around them. Several authors proposed families and segmentation of tools. The table 13 is summarizing the point of view of eight papers.

Table 13 - Eco-design tools families, based on eight papers

References	Eco-design tools segmentation

(Baumann et al., 2002)	• Frameworks • Checklists, guidelines • Rating and ranking approaches	• Analytical tools • Software and expert systems • Organizing methods
(Knight and Jenkins, 2009)	• Guidelines • Checklists	• Analytical tools
(Devanathan et al., 2010)	• Tools based on LCA • Tools based on checklists	• Tools based on QFD
(Poulikidou, 2012)	• Frameworks, guidelines and manuals for eco-design • Checklists and indices • Radar graphs and other schematic tools	• Matrix methods • Analytical Methods and tools for ED • Software and computer-based tools for ED
(Birch et al., 2012)	• Abridged (Simplified) LCA • Full LCA • Prioritization	• Material selection • Educational resources • Guidelines
(Pigosso et al., 2015)	• Product and services • CAD tools • EOL methods • Evaluation of environmental performance • Material selection • design for production optimization • System approach • R&D and product dvt integration • Information and knowledge management • Conceptual design, selection and trade-offs • KPIs • Strategic considerations • Life cycle costing • Customers and stakeholders' requirements	• Managerial integration • Development, selection and implementation of tools • Simplified guidelines and checklists • Policy and standardization • Support for SMEs • Extending lifetime and modularization • Robustness • Green marketing • Supply chain involvement • Ideation tools • Decision support systems • Monetization of envtl impacts • Portfolio management • Use-oriented design • Territorial resources
(Rossi et al., 2016)	• LCA tools • CAD integrated tools and methodology • Diagram tools • Checklists and guidelines • Design for X approaches	• Methods for supporting the company's ED implementation and generation of eco-innovation • Methods for implementing the entire life cycle and user centered design for sustainability • Methods for integrating different existing tools

(Ahmad et al., 2018)	Simple and generic tools • quantitative/time-consuming tools • preliminary qualitative analysis	4 categories • guidelines/standards • checklists • comparative tools • analytical methods

In this manuscript, two main dimensions of the Eco-design tools will be considered: the Analytical tools and the Guidance ones. Then, as displayed in the table 14, tools can be segmented in sub-categories.

Table 14 - Eco-design tools categories used in this manuscript

Tool category	Sub-category	Example
Guidance	Guidelines	UNEP Eco-design manual, The Eco-design Navigator
	Checklists	EcoDesign Checklist, Eco-design Strategy list
	Innovation	TRIZ, C-K
	Stakeholders' management	Value mapping
Analytical	Qualitative	Material selection tool, MET Matrix
	Semi-quantitative	LDfX tool
	Quantitative	LCA, MECO Matrix

- *Eco-design factor of success*

The factors of success of an Eco-design approach can be segmented through several dimensions. Boks for instance proposed two dimensions (Boks, 2006): Dissemination of information among stakeholders and Application of ecodesign principles in final product. Five Success factors split the two dimensions, with respectively Customization, Organization, Commitment for the Dissemination dimension, and Integration in business & Customization for the Application dimension. Schäfer and Löwer have identified two dimensions: the Practitioner perspective and the Research and Education one (Schäfer and Löwer, 2021).

In this manuscript, the author decided to adopt a mix between the segmentation which is close to the proposition of Boks, and subdivision proposed by Schäfer: the practitioners' dimension and the external stakeholders' one.

Practitioners' team dimension:

Success factor	Description	Reference
Strategy and management	• Product requirement at operation level • Be flexible regarding the technological and societal evolution • Implement ecodesign into management practices • Coordinate product development teams through training and by using • Gatekeepers • Set the direction for ecodesign efforts, define goals, and allocate resources • Adjust organizational structures and routines	(Schäfer and Löwer, 2021)

	• Match eco-designed products with viable business models • Nominate an environmental champion • Differentiate between process and product innovation	
Collaboration and communication	• Foster collaboration between different departments within a company and with external stakeholders • Extend collaboration along the supply chain • Implement information management systems • Share the knowledge with the right people	(Schäfer and Löwer, 2021)
Product development and design	• Provide training, tools, and methods • Change product development culture and processes • Separate the integration of environmental aspects into product development, and the integration of product development into the management system of a company" • Address environmental issues at the early stages of the product development process • Address the complete product life cycle • Circular economy • Make long-lasting, intensively used product • Focus on the customer • Customers want greener products, but won't pay more for them • Try out more radical solutions • Engage in systems thinking • Use life cycle assessment (LCA) to quantify the environmental impact of products	(Schäfer and Löwer, 2021)

Stakeholders' dimension:

When we focus on the criteria to be considered from the perspective of external stakeholders, MacDonald and She formalized seven cognitive concepts to manage in order to promote eco-design (MacDonald and She, 2015), as shown in figure 19.

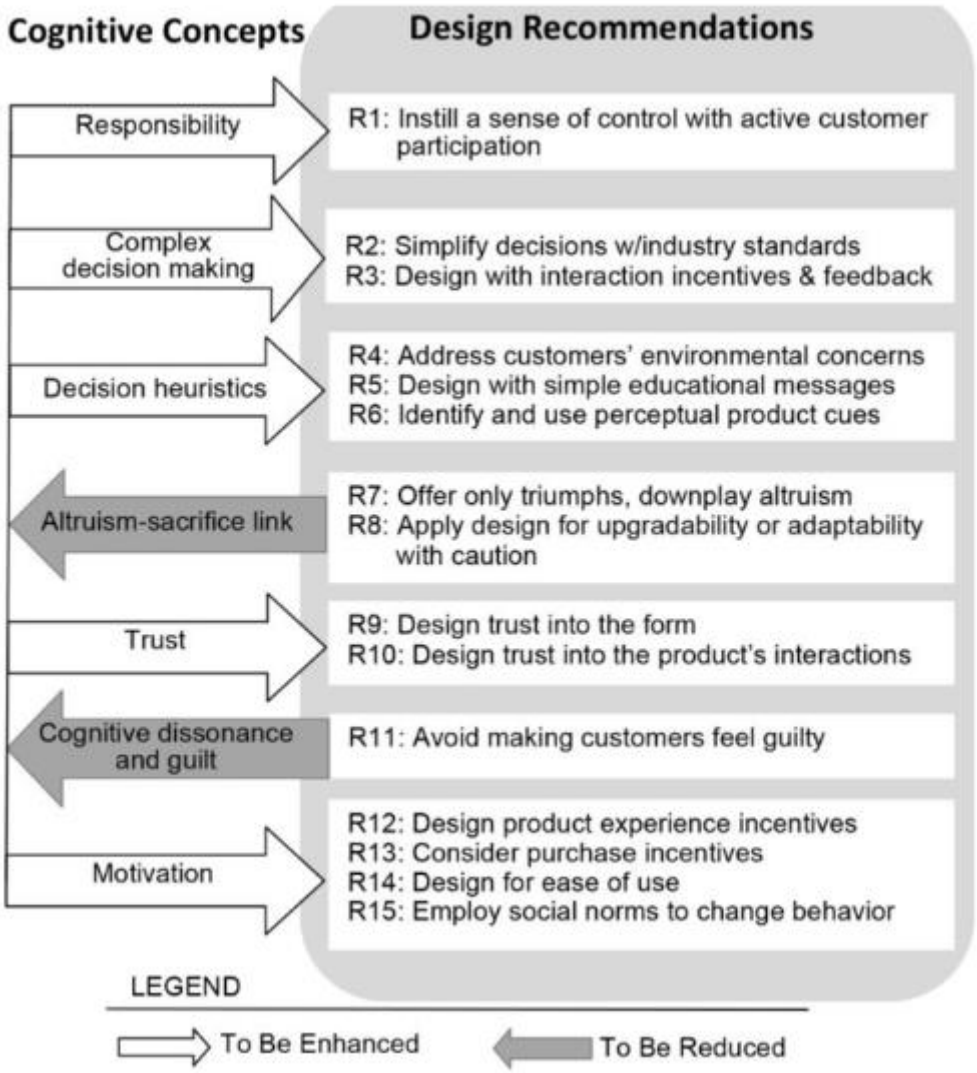


Figure 19 - Eco-design recommendations derived from the seven cognitive concepts, from MacDonald (MacDonald and She, 2015)

- *Summary of Eco-design*

Basically, the Eco-design approach could be defined as an iterative approach who consist of the assessment of the environmental footprint of a product or a service possibility, the identification and the deployment of environmental improvement. The iterative loop appears with the re-assessment of the new options.

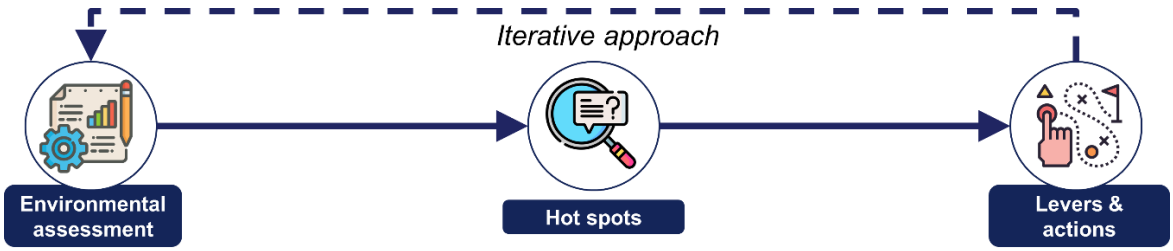


Figure 20 - Basic Eco-design approach

To perform a relevant Eco-design approach, the quantification of the holistic environmental footprint with a Life Cycle perspective and the identification of the main contributor of the environmental footprint should be supported by quantitative tools (e.g.: LCA) or semi-quantitative ones.

The identification & implementation of solutions to improve the environmental performance of the product or service can be supported by quantitative, semi-quantitative and qualitative tools (e.g.: innovation methods to foster creativity).

During this process, transversal teams need to be involved. Proper tools need to be deployed in regard of the teams involved and related culture / way of working.

II.4 Medicine product

As any products manufactured, medicines products can be Eco-designed. The point of this part is not to make an exhaustive view of them but to highlight their key aspects.

II.4.1 General overview

- *Product aspects*

In terms of design, a medicine product is usually composed of one or several Active Pharmaceutical Ingredients (API) and excipients. The mixture of the two represents the semi-finished product. This is then packaged in a container called primary then secondary packaging. The table 15 summarizes the definitions of each of the previously mentioned elements.

Table 15 - Main definitions linked to a medicine product

	Definition	Example
Active Pharmaceutical Ingredients (API)	Substance of chemical or natural origin characterized by a specific curative or preventive mechanism of action in the body or allowing to establish a medical diagnosis or to act on the physiological functions	Paracetamol, aspirin, ibuprofen
Excipient	Substances of chemical or natural origin which facilitate the use of the drug but do not have a curative or preventive effect	Saccharose, lactose, magnesium stearate
Semi-finished product	Product resulting from all the operations preceding the packaging of a production	Paste, tablet, liquid
Galenic form	State in which the constituent elements of a medicinal product are combined. Is both a system of presentation, sometimes storage of the drug and provision of the active substance to the patient's body. Is an essential element of patient acceptability (compliance), efficacy, proper use and safety of use of the drug (possible dose adjustment)"	Ointment, cream, tablet, syrup, gels, etc
Primary packaging	Packaging in direct contact with the drug. It has a protective role *(humidity, light, air, biological contamination, etc.)*, functional *(facilitating use, increasing safety, etc.)*, identification and information *(batch number, trade name, etc.)*	Blister, bottle, syringe
Secondary packaging	Packaging protecting the primary packaging and not in contact with the drug. Can also have a protective, functional, identification and informational role	Carton, blister

Through the previous elements, it is possible to understand that there is a typological diversity of forms of drugs. The primary role of this type of product is to treat (heal, cure or diagnosis) patients. Two drugs, with different APIs and in different forms can treat the same disease. We are thus faced with a problem of drug classification that must both integrate the notions of therapeutic areas as well as those of product design.

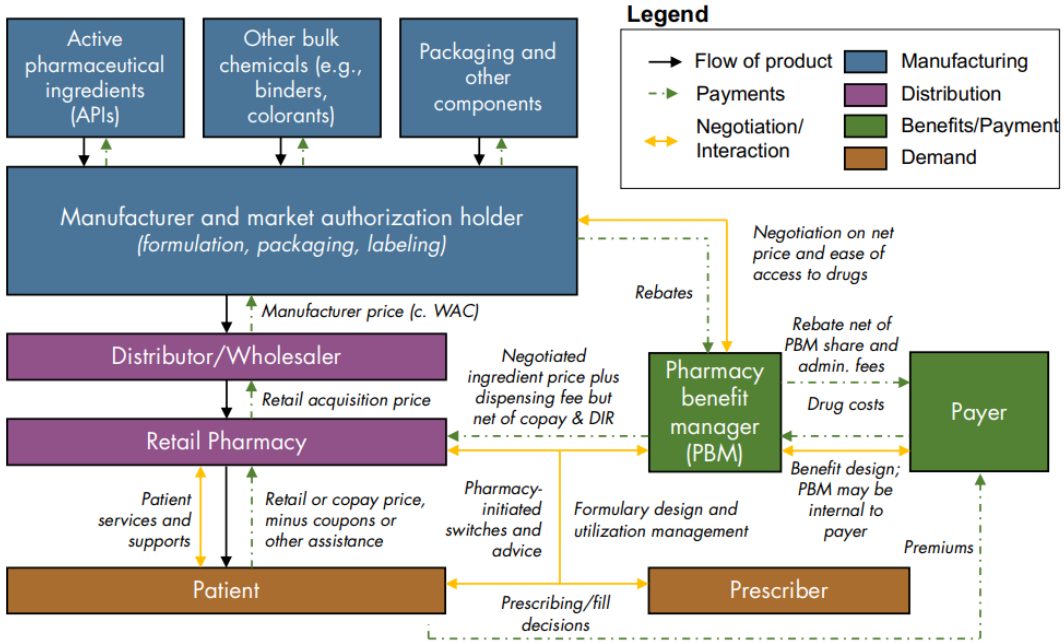
To meet these two challenges, there are two main classifications of drugs, complementary and internationally recognized, the Anatomical Therapeutic Chemical (ATC) and the European Pharmaceutical Marketing Research Association (EphMRA) classification. The following table summarizes the main features:

Table 16 - Medicine classifications

Classification name	ATC	EphMRA (EPhMRA, 2019)
Entity in charge of the classification	World Health Organization	European Pharmaceutical Marketing Research Association
Structure	5 levels: 1. Target organs or systems 2. Therapeutic subgroups 3. Pharmacological subgroups 4. Chemical groups 5. Chemical substances	3 levels: 1. Systemic and topical effect, route of administration, long and ordinary forms 2. Galenic form 3. Subdivision of the dosage form
Classification format	Letters and numbers: e.g., N02BE01 = Paracetamol	Three letters: e.g., BCA = Oral; Solid; Delayed effect capsules
Targeted public	Education, clinical trials, health organizations and government	Marketing, marketing research
Vocation	Substance classification	Product classification

- *Lifecycle perspective*

The lifecycle of a medicine includes steps from the raw material required to the production, to the end-of-life of the product after patient consumption, including all the supply chain around the product. Figure 21 is presenting a generic overview of such lifecycle, with example of stakeholders.



NOTES: c. = circa; DIR = direct and indirect remuneration; WAC = wholesale acquisition cost. Arrows denote relationships involving the flow of product (black arrows), information or negotiation (yellow arrows), and payments (green dashed arrows).

Figure 21 - Generic supply chain for brand-name drugs dispensed through retail pharmacies, from Mulcahy and Kareddy (Mulcahy and Kareddy, 2021)

II.4.2 Active Pharmaceutical Ingredient (API)

The API is the most important constituent of a medicine product. It can be obtained chemically, or through biologics, which includes microbiological or cell culture as well as by extraction from plant or animal tissue. An active ingredient derived from a microbiological culture or from plant or animal tissues can, after extraction, be combined with chemical syntheses.

The steps per type of API synthesis processes differ depending on the product. For example, to produce a chemical molecule, it is possible to have different synthesis pathways, generating several heating steps, mixtures, or even different consumption of reagents.

Historically, chemistry was the base of traditional medicine. However, biologics represent much more potential for the treatment of cancer, autoimmune diseases, and inheritable diseases (Ngo and Garneau-Tsodikova, 2018). The terminology biology includes a range of categories.

The Food and Drug Administration (FDA) defines a biological product as *"a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs"* (FDA, 2022). They are including products such as *"vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins"* (Center for Biologics Evaluation and Research, 2019).

The European Medicines Agency (EMA) proposes the definition of biological medicinal product below: *"product that contains a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physico-chemical-biological testing together with the production process and its control"*. They are considering *"recombinant proteins, monoclonal antibodies, medicinal products derived from human blood and human plasma, immunological medicinal products and advanced therapy medicinal products"* as such (EMA, 2019).

In fact, several other categories could fit to the generic definition of biological API proposed by both the FDA and the EMA. The table 17 is the author suggestion of biological API.

Table 17 - List of biological API

Category	Description	Reference
Blood derivatives	"any therapeutic substance derived from human blood, including whole blood and other blood components for transfusion, and plasma-derived medicinal products"	(Starr, 2012; WHO, 2022)
Cellular therapy	"transfer of autologous or allogeneic cellular material into a patient for medical purposes"	(El-Kadiry et al., 2021)
Monoclonal antibodies	"laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on cancer cells"	(Bayer, 2019)
Conjugated monoclonal antibodies	"highly targeted biopharmaceutical drugs that combine monoclonal antibodies specific to surface antigens present on particular tumor cells with highly potent anti-cancer agents linked via a chemical linker"	(ADC, 2019)
Interferons	"proteins that belong to the group of signaling molecules known as cytokines involved in the upregulation of the immune response"	(Khanna and Gerriets, 2022)
Growth factors	"biologically active molecule that can affect the growth of cells and molecules that promote or inhibit mitosis or affect cellular differentiation"	(Stone et al., 2022)
Peptides	"molecule that contains two or more amino acids (the molecules that join together to form proteins)"	(NCI, 2011; Wieland and Bodanszky, 2012)

Gene therapy	"Biological medicinal product which fulfils the following two characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence"	(Wirth et al., 2013)
RNA therapy	"use of RNA-based molecules to modulate biological pathways to cure a specific condition"	(Kim, 2022)
Whole pathogen or live attenuated vaccines	"pathogens that have been weakened, altered or selected to be less virulent than their wild-type counterparts. In their altered form, they cannot cause the actual disease or only mimic the disease in a very mild way. [These] vaccines are generally produced from viruses rather than bacteria because viruses contain fewer genes and attenuation can be obtained and controlled more reliably"	(Vetter et al., 2018)
Inactivated vaccines	"[Inactivated] preparations of whole pathogens by heat, radiation, or chemicals such as formalin or formaldehyde. Inactivation destroys the pathogen's ability to replicate and cause the disease but maintains its immunogenicity, so that the immune system can still recognize the targeted pathogen"	(Vetter et al., 2018)
mRNA vaccines	"mRNA is the intermediate step between the translation of protein-encoding DNA and the production of proteins by ribosomes in the cytoplasm. Two major types of RNA are currently studied as vaccines: non-replicating mRNA and virally derived, self-amplifying RNA. Conventional mRNA-based vaccines encode the antigen of interest and contain 5′ and 3′ untranslated regions (UTRs), whereas self-amplifying RNAs encode not only the antigen but also the viral replication machinery that enables intracellular RNA amplification and abundant protein expression"	(Pardi et al., 2018)
Subunit, recombinant, polysaccharide, and conjugate vaccines	"Subunit, recombinant, polysaccharide, and conjugate vaccines use specific pieces of the germ—like its protein, sugar, or capsid (a casing around the germ). Because these vaccines use only specific pieces of the germ, they give a very strong immune response that's targeted to key parts of the germ. They can also be used on almost everyone who needs them, including people with weakened immune systems and long-term health problems. One limitation of these vaccines is that you may need booster shots to get ongoing protection against diseases."	(U.S. Department of Health & Human Services, 2021)
Toxoid vaccine	"Toxoid vaccines use a toxin (harmful product) made by the germ that causes a disease. They create immunity to the parts of the germ that cause a disease instead of the	(U.S. Department of Health & Human Services, 2021)

	germ itself. That means the immune response is targeted to the toxin instead of the whole germ."	
Viral vector vaccines	"Viral vector vaccines use a modified version of a different virus as a vector to deliver protection. Several different viruses have been used as vectors, including influenza, vesicular stomatitis virus (VSV), measles virus, and adenovirus, which causes the common cold."	(U.S. Department of Health & Human Services, 2021)

The complexity of API manufacturing will imply technologies depending on myriads of factors. Even if it is not possible to set generalities, the table below gives an overview of technologies / process related to examples for organic chemistry and cell culture-based APIs. The table do not provide an exhaustive list, it aims to highlight the complexity of API production. For instance, for flow chemistry, purification steps could be required. This necessity of purity increase will imply a range of purification types, which themselves will call for different technologies. In the Eco-design mindset, each of such technology will have their own environmental profile, which remain to be determined from an LCA perspective.

Table 18 - Non exhaustive examples of potential technologies, related to process / step of specific API family

Family of API	Process /step	Potential technologies	Reference
Organic chemistry	• Flow chemistry	• Heating / cooling systems • Pumps • Distillation columns • Microreactor • Thermal or photoreactor • Micromixer • Pressure regulator • Process stacks • Robotic arm • Tubing reels • In-line evaporation • Purification	(Baumann et al., 2020; Fanelli et al., 2017; Guidi et al., 2020; Porta et al., 2016)
	• Purification	• Ion-exchange resins • Selective cleavage • Dialysis • Ultrafiltration • Size-exclusion chromatography • Precipitation/filtration • Liquid-phase separation	(Tzschucke et al., 2002)
Cell culture	• Fermentation	• Pumps • Fermenter • Bioreactor • Automation systems • In-process analysis instruments • Single Use Assemblies	(Conner et al., 2014; Luu et al., 2022)
	• Bioreactor	• Pumps • 10,000L bioreactor • Single Use Assemblies	(BioPharm International Editors, 2022; Luu et al., 2022)
	• Harvesting and isolation	• Pumps • Centrifugation • Cellulose based filter media	(Haupt et al., 2012; Najafpour, 2007)

	• Microfiltration • Single Use Assemblies	
• Purification, Virus removal / inactivation	• Pumps • Filtration • Chromatographic columns • Tangential flow filtration • Single Use Assemblies	(Conner et al., 2014)

II.4.3 Galenic forms & packaging

As previously, it is interesting to have a look on the different typology of the galenic forms and, as there are intrinsically linked, to the different primary packaging.

The exploitation of a data extraction from French organizations names the High Authority of Health (HAS), the National Agency for the Safety of Medicines (ANSM) and the Health Insurance (AM), makes it possible to have a visibility on 15 045 referenced products (ANSM et al., 2020). The following figure summarizes the distribution of the majority dosage forms. The term "other" includes all routes of administration accounting for 1% or less of the products referenced.

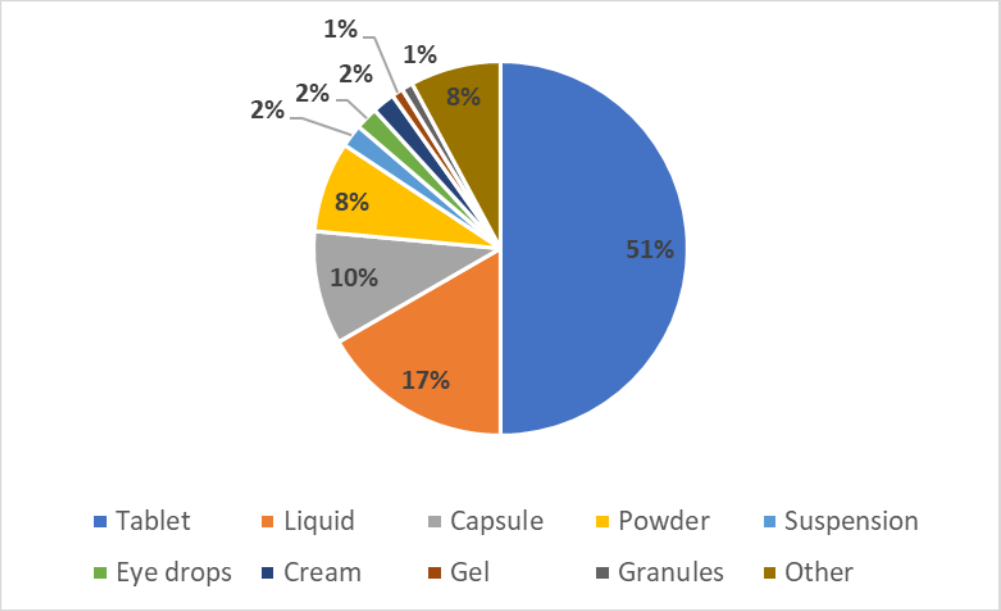


Figure 22 - Repartition of the galenic formulation available in France, based on 15 045 references in 2020

The EPhMRA classification propose seven main categories of galenic forms with in total 22 sub forms. The table 19 summarize them.

Table 19 - EPhMRA second letter classification regarding the galenic form

Family	Second letter	Category
Solid forms	A	Tablets
Solid forms	B	Coated Tablets
Solid forms	C	Capsules
Solid forms	D	Solid Special Forms
Solid forms	E	Powders/Granules
Gases	F	Gases
Liquids	G	Liquids
Liquids	H	Pressurized Aerosols

Liquids	J	Bath Preparations
Liquids	K	Teas
Suppositories	L	Suppositories
Injections	M	Ampoules
Injections	N	Pre-filled Syringe
Injections	P	Vials
Injections	Q	Infusions
Injections	R	Cartridges/Pens
Ointments	S	Ointments
Ointments	T	Creams
Ointments	V	Gels and Sols
Others	W	Medicated Dressings
Others	Y	Other Special Forms
Others	Z	Medical Aids

Despite the philosophy of the classification to provide with the second letter galenic formulation, we can see that for the injection form, most of the proposition are linked to the primary packaging. It is also possible to merge the "ointments" category with the "suppositories" one, which are usually considered as "semi-solid" in the pharmaceutical industry.

The different tables summarize non exhaustive list of them, related to high level steps of each of the four main galenic form family described previously (Collectif, 2016).

Table 20 - Potential technology & process related to the steps of a solid form of medicine product

Step	Powder preparation	Mix process	Galenic formulation	Packaging
Potential technology / process	• Weighting • Grinding • Sieving	• Compound for direct compression • Dry granulation • Wet granulation in mixer • Fluidized bed granulation • Drying • hot melt extrusion • Calibration • Spheroid • Atomization / Instantization / Prilling • Sparkling mix • Final mix: lubrication - homogenization • Confinement	• Transfer • Compression • Filling capsules • Coating • Microencapsulation	• Thermoformed blister • Cold formed blister • Bag • Strip-Seal • Glass pill box • Plastic pill box • Aluminum pill box • Box • Roll • Bulk • Glass bottle • Plastic bottle

Table 21 - Potential technology & process related to the steps of a semi-solid form of medicine product

Step	Galenic formulation	Packaging preparation	Packaging
Potential technology / process	• Lip or water-soluble preservative • Oily or aqueous phase	• Unpacking • Blowing • Washing • Drying	• Aluminum tube • Plastic tubing • Glass or plastic jar • Suppository

	• Active ingredient • Perfume / aroma • gelling agent • Solution • Charge	• Sterilization - container • Filtering - content • Filling • Inerting • Corking • Screwing • Crimping • Folding • Sealing • Coding • Sterilization • 100% integrity check • Mirage • Continuous weight control • Labeling	• Patch • Gauze • Blister

Table 22 - Potential technology & process related to the steps of a liquid form of medicine product

Step	Galenic formulation	Packaging preparation	Packaging
Potential technology / process	• Filling • Mix • Dispersion • Homogenization • Filtration • In-line homogenization • Storage	• Unpacking • Blowing • Washing • Drying • Sterilization - container • Filtering - content • Filling • Inerting • Corking • lidding • Screwing • Crimping • Sealing • Coding • Sterilization • Integrity check on containers • Mirage • Labeling	• Aluminum tube • Plastic tubing • Glass or plastic jar • Suppository • Patch • Gauze • Blister

Table 23 - Potential technology & process related to the steps of an injectable form of medicine product

Step	Water (purified or for injection)	Galenic formulation	Packaging preparation	Packaging
Potential technology / process	• Reverse osmosis • Ion exchange resins • Distillation by multiple effects	• Filling • Mix • Dispersion • Homogenization • Filtration	• Depacker • Washer • Sterilization and depyrogenization tunnel	• Glass bottle • Plastic bottle • Pen • Plastic bulb

	• Thermocompression distillation • Membrane techniques (ultrafiltration) • Loop concept • Storage	• In-line homogenization • Storage • Freezing • Sublimation or primary desiccation • Secondary desiccation	• Filler • Freeze dryer • Sterilizer • Corker • Mirage • Capper • Labeler	• Bulb glass bottle • Pre-filled syringe • Soft pocket • Infusion glass bottle • Plastic infusion bottle • 2-point injectable ampoule • Carpules

II.4.4 Distribution, use and end-of-life

Distribution

The supply chain represents a significant element in the product life cycle. Air transport will thus significantly increase the carbon footprint of the product compared to sea freight, train or road transportation. In the same way, the storage conditions in order to guarantee the integrity of the drug will come to add a weight on the environmental footprint of this one. Usually, medicines production plants feed wholesalers who supply then either hospitals or pharmacies. In some cases, pharmaceutical factories can directly send products to hospitals or pharmacies. The figure below summarizes the flows mentioned with transportation who might be used in France. The percentage are the one related to the specific flow, for instance, 20,3% of the volume from the pharmaceutical factory supply directly hospitals. It can be by boat, plane, train, or truck.

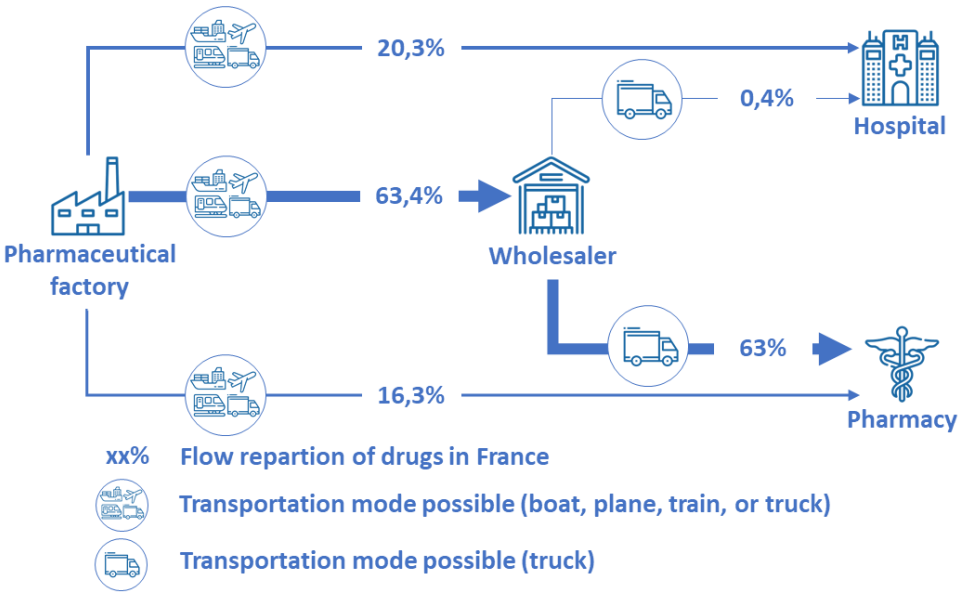


Figure 23 – French repartition of drug distribution circuit with the potential transportation mode (Turan-Pelletier and Zeggar, 2014)

Use and end-of-life

Depending on the typology of medicine, patient can either go to hospital, get a prescription from a physician before get medicine in pharmacy, or buy directly Over the Counter (OTC) drugs.

Usually, the application, administration, or consumption can either be done in hospital, at the pharmacy (e.g., vaccines in France) or in a private place such as patient homeplace. As described in the figure below, patient can either use motorized transportation like car, two wheels vehicle or public transportation, bike, or even walk.

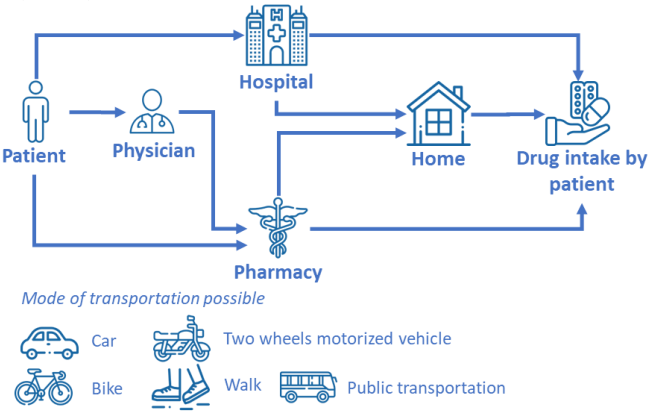


Figure 24 – Main potential patient circuit to get access to a drug

Even if some countries could have specificities regarding the end of life, when a patient intake a medicine, metabolites can be expected in secretions. Either in the sweat, which will be wash-off in shower, or in feces or urines.

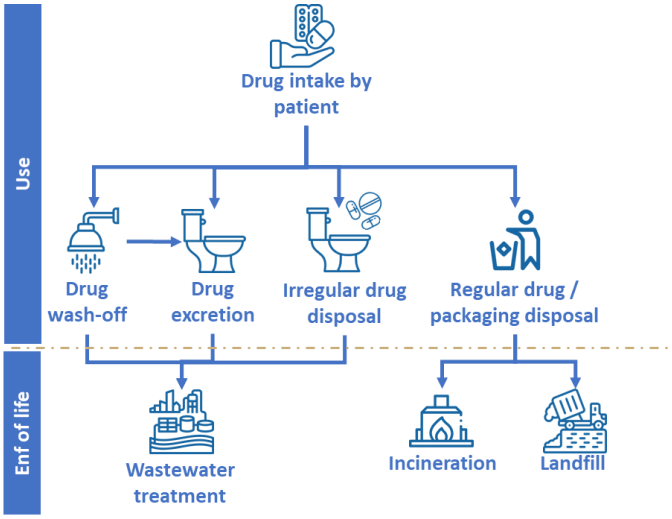


Figure 25 - Use and End of life phases, based on Siegert (M. Siegert et al., 2020)

II.5 Environment and pharmaceutical products

Like any Human activity, the production and the consumption of medicine products do impact the environment. In this part, description of current knowledge regarding the environmental impacts of such products is described.

II.5.1 Pharmaceutical products contribution in the environmental health-care system footprint

Lenzen et al. performed in 2020 a study to assess the overall environmental footprint of the health-care system. They *"evaluated the contribution of health-care sectors in driving environmental damage that in turn puts human health at risk. Using a global supply-chain database containing detailed information on health-care sectors,* [they] *quantified the direct and indirect supply-chain environmental damage driven by the demand for health care.* [they] *focused on seven environmental stressors with known adverse feedback cycles: greenhouse gas emissions, particulate matter, air*

pollutants (nitrogen oxides and sulfur dioxide), malaria risk, reactive nitrogen in water, and scarce water use." (Lenzen et al., 2020). They highlighted that health-care system is contributing between 1% and 5% of total global impacts, depending on the indicator, as shown in the figure below.

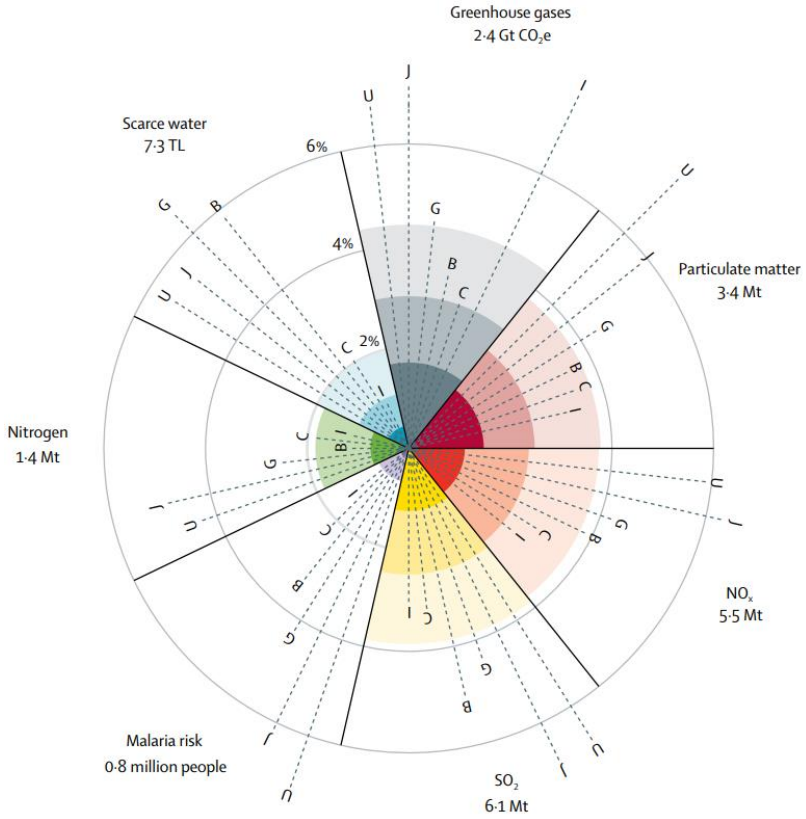


Figure 26 - Contribution of the health-care system in several environmental indicators .The impact is shown as a percentage of total impact, for the world (segments) and selected countries (spokes), in terms of greenhouse gas emissions (global total=54.4 Gt CO2e), particulate matter (12.2 Mt), NOx (161.9 Mt) and SO2 (167.3 Mt) emissions, malaria risk (113.1 million people), nitrogen to water (79.0 Mt), and scarce water use (483.9 TL). Spokes represent data for the USA (U), Japan (J), the UK (G), Brazil (B), China (C), and India (I). Direct (lightest shade), first-order (middle shade), and supply-chain (darkest shade) refer to impacts caused by health care directly, by health care's immediate suppliers, and the remainder, respectively. From Lenzen et al (Lenzen et al., 2020)

In the same study, the authors presented the breakdown of the health-care system carbon emissions, displayed in the figure 27. By including the items "medicaments" (3.6 Mt CO2-eq), "Medical and pharmaceutical products" (23.9 Mt CO2-eq), "Pharmaceutical companies" (6.1 Mt CO2-eq), and "Drugs" (2.6 Mt CO2-eq), the overall contribution of the pharmaceutical sector in 2015 was around 36.5 Mt CO2-eq, representing 15% of the footprint of the health-care system.

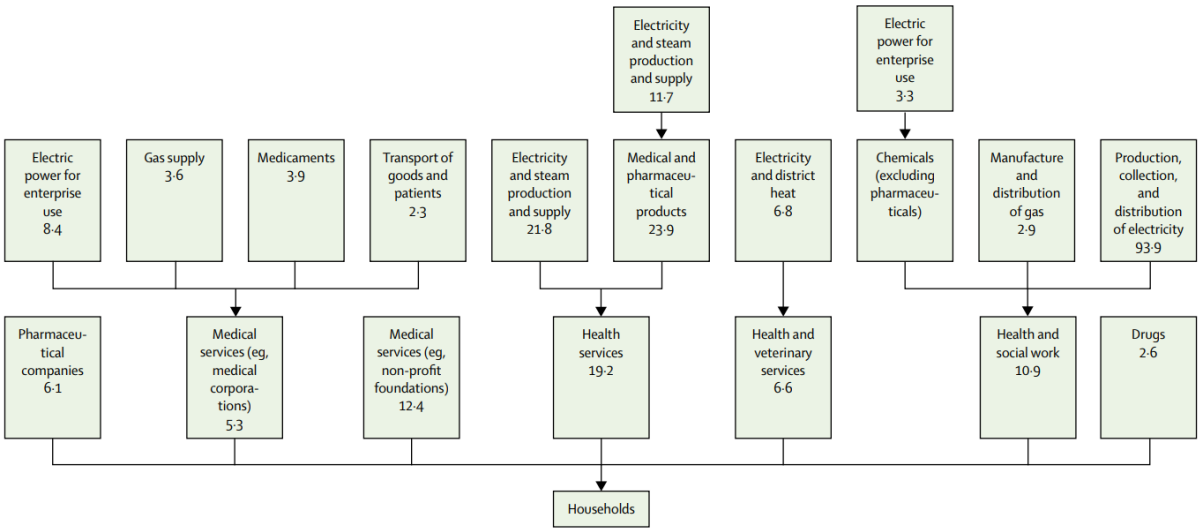


Figure 27 - Breakdown of the health-care system carbon emissions, in megatons of carbon dioxide equivalent, from Lenzen et al (Lenzen et al., 2020)

Eckelman et al. conducted a similar study but with another approach, with a focus on Canada, assessing the health-care system carbon emission between 2009 and 2015 (Eckelman et al., 2018). They were able to demonstrate that GHGs of the health-care system were stable and around 4.5% of the overall GHGs of Canada, as illustrated in the table 24.

Table 24 - GHG emissions of Canada and contribution of its health-care system

	2009	2010	2011	2012	2013	2014	2015
Total GHGs (MtCO2-eq)	29.6	31.2	31.4	31.5	31.4	32	33
Health-care GHGs (MtCO2-eq)	682	694	700	707	716	716	714
% Health-care GHGs	4.3%	4.5%	4.5%	4.4%	4.5%	4.5%	4.6%

However, the profile of the breakdown is not similar. In the authors study, the pharmaceutical industry is contributing at 3% of the Canadian health-care system emissions. But as the methodologies are not the same, it is not possible to compare the relatives' figures from each study.

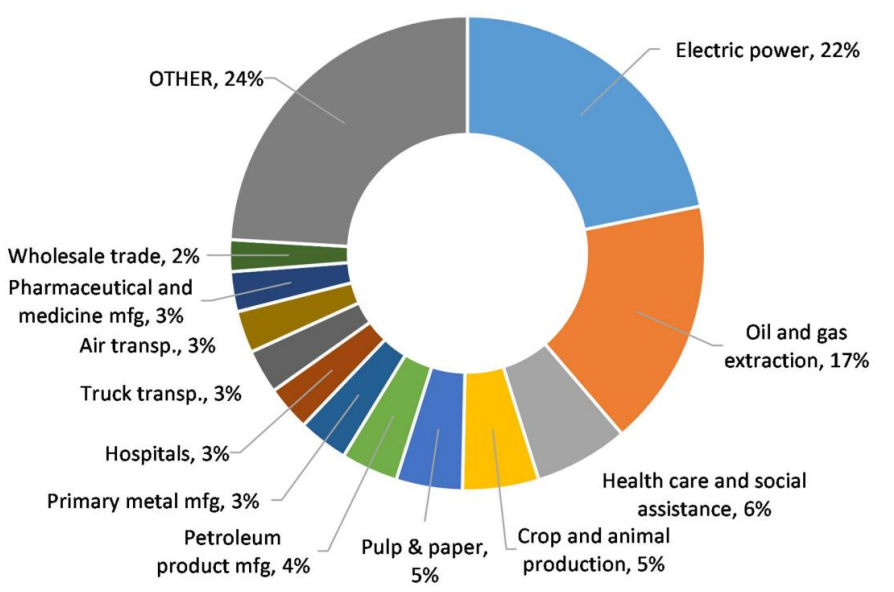


Figure 28 - Breakdown of the GHGs contributors of the Canadian health-care system, from Eckelman et al. (Eckelman et al., 2018)

The National Health Service (NHS) of the United Kingdom (UK) launched July 1st, 2022, a roadmap to decarbonate the health-care system of the UK. In a report (NHS, 2022), they estimated for 2020 a decrease of 62% of their carbon footprint, regarding the emissions of 1990, as illustrated in the figure below.

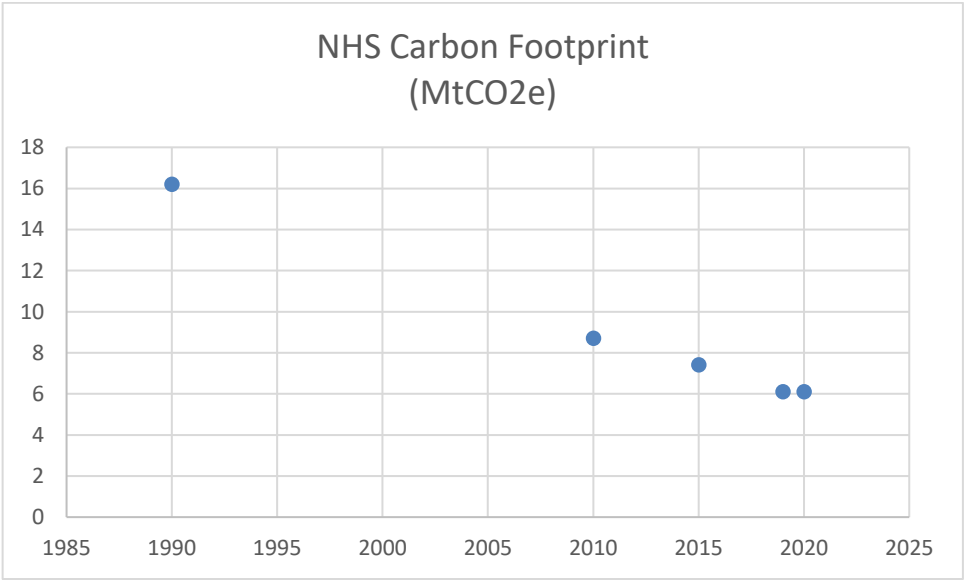


Figure 29 - NHS emissions from 1990 to 2020, adapted from NHS (NHS, 2022)

In the same study, the NHS highlighted the breakdown of the GHG contributors of the UK health-care system, illustrated in the figure 30. Based on their methodology of calculation, they estimated that “medicines & chemicals” coming as a second contributor, at 20% of the health-care system footprint, behind what they identified as “other supply chain”.

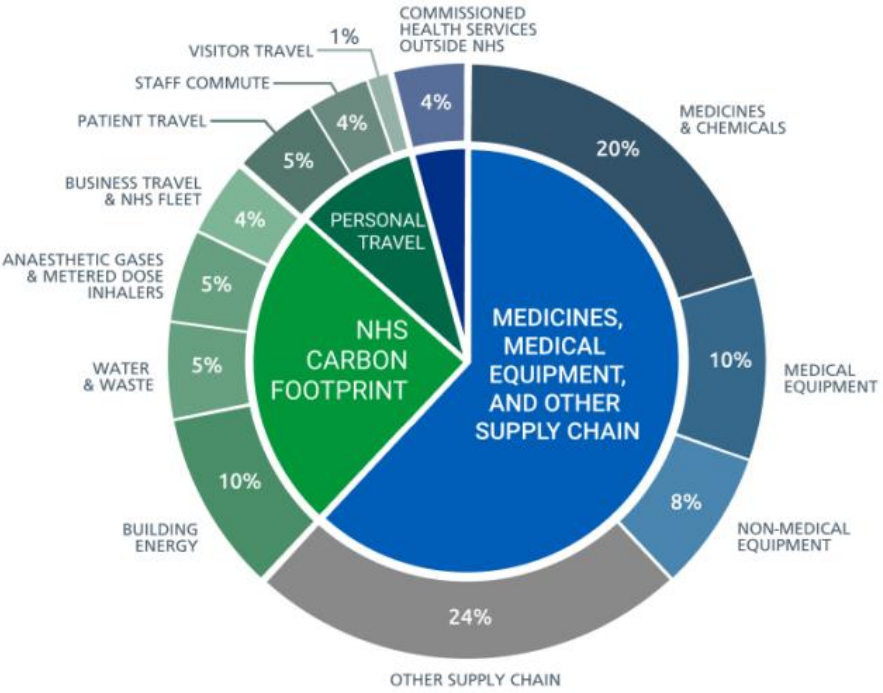


Figure 30 - Breakdown of the GHGs contributors of the UK health-care system, from Eckelman (NHS, 2022)

In France, a similar study was released on November 25th, 2021. It was conducted by the Shift project, a French think tank who aim to foster the decarbonation of the French activities. They estimated that the contribution of the pharmaceutical industry (included in the category "purchase of drugs") contributed to 33% of the health-care system GHG emissions, as illustrated in the figure 31 (The Shift Project, 2021).

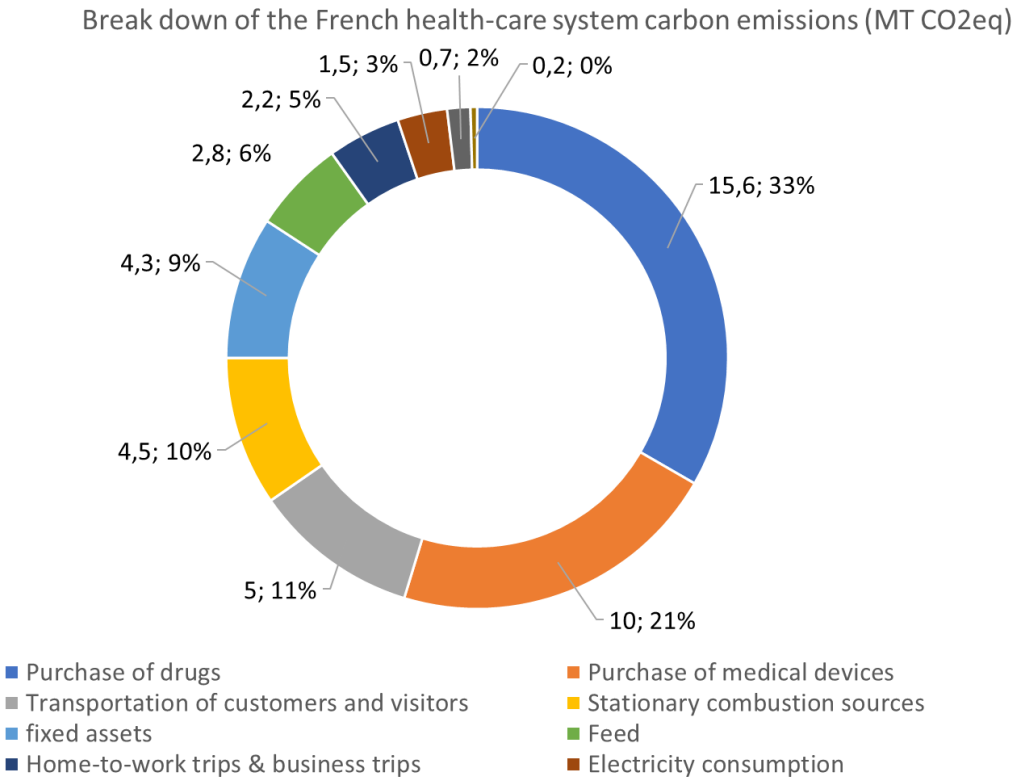


Figure 31 - Breakdown of the GHGs contributors of the French health-care system, adapted from the Shift project (The Shift Project, 2021)

However, it can be noted that no representative of the pharmaceutical industry was included in this assessment which was based on an economic assumption. Indeed, they based the calculation with an emission factor (EF) from the French agency ADEME, which considers for medicine an EF around 0.5403 kgCO2-eq / €.

Table 25 summarizes the estimations exposed previously.

Table 25 - Contribution of the pharmaceutical industry within the GHG emissions of health-care systems, by geographic scope

Geographic scope	Year	Contribution of the pharmaceutical industry in the GHG emissions	Methodological approach	Reference
World	2015	15%	Multiregional input-output analysis	(Lenzen et al., 2020)
Canada	2015	3%	Input-output + LCA (IMPACT2002+)	(Eckelman et al., 2018)
UK	2020	20%	Economic allocation	(NHS, 2022)
France	2019	33%	Economic allocation	(The Shift Project, 2021)

Even if the ranges of values are interesting to compare, as the approaches of the different authors are not the same, results are not comparable. It remains an information to get a high-level understanding of the contribution of the pharmaceutical industry within the GHGs emissions of the health-care systems under the studies.

II.5.2 Pharmaceutical products environmental specific concerns

Medicine products are made with compounds with an activity for humans or animals. Those compounds are called Active Pharmaceutical Ingredient (API) and, as product with a potential release & toxicity for the environment (Taylor and Senac, 2014), can be consider as New Entities in the Planetary Boundaries framework (Persson et al., 2022; Rockström et al., 2009).

Some trace of consideration of API of medicine and related metabolites as pollution for the environment can be found around 1970 (Hignite and Azarnoff, 1977) and are nowadays raised as a major concern to the environment (Wilkinson et al., 2022) from such products. In the Eco-design approach, those elements are only a part of the environmental impact of such product. For instance, in the COVID-19 vaccines case, 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). In other words, 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. Souza et al. have described in their paper links between the environmental issues related to medicine and the SDGs, as illustrated in the figure below (Souza et al., 2021).

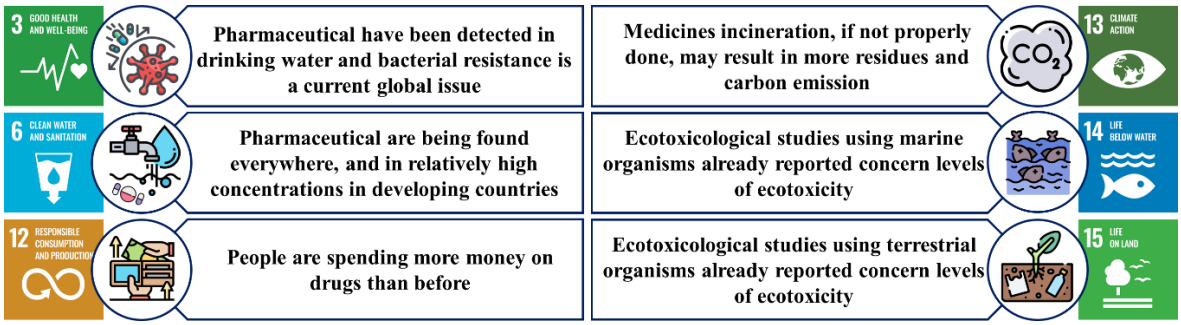


Figure 32 – Example of environmental issues of medicine linked to SDGs, adapted from Souza (Souza et al., 2021)

The pharmaceutical industry is mainly focused on safety and effectiveness of drugs, but it does not make an exception on the sustainability topic. 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.

II.5.3 Pharmaceutical products Life Cycle Assessment

- *Overview of the studies available in the literature*

LCA is not a new approach in the pharmaceutical sector. However, it is not well embraced. 63 papers related to LCA and the pharmaceutical industry were identified, as illustrated in the chronology of the figure 33.

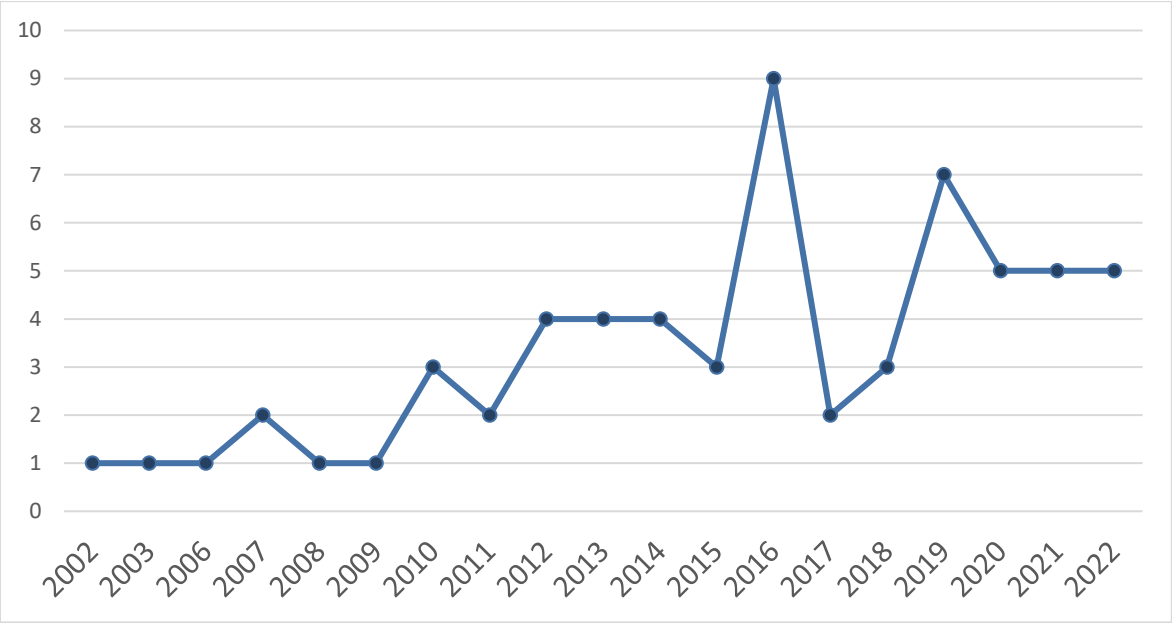


Figure 33 - Distribution of the papers related to LCA and the pharmaceutical sector assessed, between 2002 and 2022

Within these papers, 48 were identified as LCA studies per se, with comparative assessment or multiple products in the same paper. Witness of the maturity of this approach in the pharmaceutical sector, none of these papers were describing the function of the product or service under study. Only one paper is mentioning a Reference flow and 46 did not formalized the Functional Unit (FU). The table 26 is presenting the "families" of FU defined in the different papers and the description of them.

Table 26 - Repartition of FU families used in the different studies of the papers assessed

FU families	Description	Number of assessments with the FU
None	No FU formalized	49
Batch oriented	FU defined to fit the production of a batch (e.g.: API required to produce one hundred thousand paracetamol tablets)	34
Function oriented	FU defined to suit the function of the product or service (e.g.: treatment of an adult in Germany with the purpose of pain relief for 4 days)	8
API oriented	FU defined to focus on API production (e.g.: production of 1 kg sildenafil citrate)	7
Product oriented	FU defined to fit the technical characteristics of the product or service (e.g.: set of operations required to Fill and Finish (F&F) a 20 ml vial, stoppered, and capered which contains 608.8 mg of freeze-dried infliximab powder (including excipients)).	6
Patient oriented	FU defined to suit the use, from a patient perspective (e.g.: delivery of 1 dose of inhaled medicine)	4

The appendix 2 is presenting the list with the scope of each study. We can observe that for 67% of them, a cradle-to-gate perspective and 18% gate-to-gate as shown in figure 34 was used. These scopes might explain the preponderance of the FUs with a batch-oriented approach.

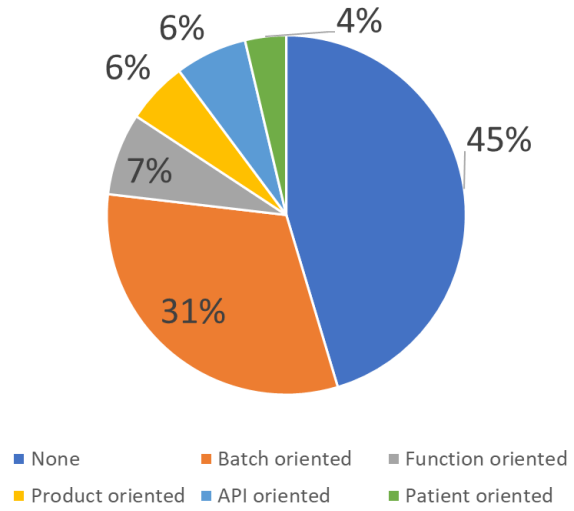


Figure 34 - Repartition of the scope of the LCAs under the assessment

The literature present mainly LCAs regarding “APIs” (56%). The 25% for the “Process” can be explain by the fact that one study was displaying a detailed breakdown of its results, with several steps of a tablet galenic formulation. If we consider this as only one study, there are in fact only two studies for the “Process”. The “Device” was studied in 8% of the papers where 4% were focused on “Packaging”. Finally, 7% of the studies had waste at manufacturing levels (e.g.: solvent), or at end of life of the product (e.g.: wastewater treatment plant, incineration of medicine), which are included in “Waste or end of life”.

Within the APIs studies, 78% of them were focused on chemicals-based one, 13% on enzyme, 7% on monoclonal antibody and only one on conjugated protein, as shown in the figure 35.

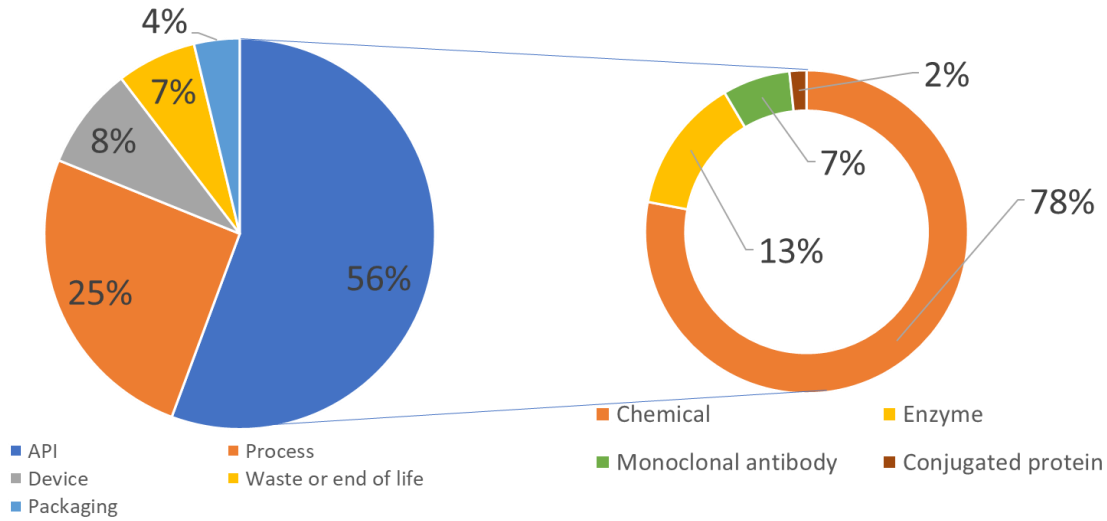


Figure 35 - Repartition of the LCAs focus, with the details for the APIs ones

- *Overview of the results for the IPCC GWP 100a (kg CO2 eq) indicator*

As described by Emara, discrepancy can be found regarding the Life Cycle Impact Assessment (LCIA) used within the different studies (Emara et al., 2018). However, one constant is observable for most of them, the use of the IPCC GWP 100a (kg CO2 eq) indicator.

Even if the focus on Climate change is only one part of the overall environmental picture, it is possible to set ranges of kg CO2 eq of families of APIs, from the papers assessed as illustrated in the table 27. The appendix 3 is presenting all the kg CO2 eq results values for each focus who are presents in the papers.

Table 27 - Ranges of emissions in kg CO2-eq / kg per API family

API family	Minimum (kg CO2 eq / kg)	Maximum (kg CO2 eq / kg)	Average (kg CO2 eq / kg)	Standard deviation	Number of values
Chemical	2.06	3006	386.7	744.5	32
Enzyme	1	25	11	9.3	8
Monoclonal antibody	20000	276600	97506	111442	5

II.5.4 Current environmental practices in the pharmaceutical industry

Despite the fact that the pharmaceutical industry does not seems to have embraced fully the Eco-design journey, they do integrate environmental aspects into their activity. This chapter aims to describe some key approaches deployed by this sector.

- *Green chemistry*

It will be unfair to talk about the environmental sustainability approaches of the pharmaceutical sector without talking about Green chemistry. Anastas consider the birth of the Green chemistry in close relation with the Pollution Prevention Act of 1990, which aimed to prevent the environmental issues in the United States soil (Anastas and Williamson, 1996). The Green chemistry is based on 12 key principles which are listed in the table 28:

Table 28 - The 12 principles of Green chemistry, based on Anastas (Anastas and Williamson, 1996)

Principle n°	Title	Main philosophy
1	Prevent waste	It is better to prevent waste than to treat or clean up waste after it is formed
2	Atom economy	Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product
3	Less hazardous synthesis	Wherever practicable, synthetic methodologies should be designed to use and generate substances that process little or no toxicity to human health and the environment
4	Design benign chemicals	Chemical products should be designed to preserve efficacy of function while reducing toxicity
5	Benign solvents & auxiliaries	The use of auxiliary substances (e.g.: solvents, separation agents) should be made unnecessary wherever possible and innocuous when used
6	Design for energy efficiency	Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure
7	Use of renewable feedstocks	A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable
8	Reduce derivatives	Unnecessary derivatization (e.g.: blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible
9	Catalysis (vs stoichiometric)	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents

10	Design for degradation	Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products
11	Real-time analysis for pollution prevention	Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances
12	Inherently benign chemistry for accident prevention	Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires

Based on those principles, the American Chemistry Society (ACS) made available several tools to the community. The table 29 is presenting them.

Table 29 – Green chemistry tools made available by the ACS

Title	Type of tool	Description	Reference
Reagent guides	Guidance – guideline	Guideline with qualitative guidance to advice chemist in what is considered as environmentally sustainable reaction conditions	(Bryan et al., 2013)
Biocatalysis guide	Guidance – guideline	Guideline with qualitative guidance to advice chemist in what is considered as environmentally sustainable biocatalyst	(Sheldon and Woodley, 2018; Turner and O'Reilly, 2013)
Solvent selection tool	Guidance – guideline	Originally developed by AstraZeneca, this tool score solvents, based on the Principal Component Analysis (e.g.: physical properties, functional groups)	(Diorazio et al., 2016; Prat et al., 2014)
Solvent selection guide	Guidance – guideline	Guideline developed based on Health, Safety, and Environmental criteria of solvents	(Alder et al., 2016)
Process Mass Intensity (PMI) prediction calculator	Analytical – semi-quantitative	Analytical tool with a gate-to-gate perspective. It allows the calculation of PMI and comparisons with historical data available	(Borovika et al., 2019)
PMI calculator	Analytical – Quantitative	Quantitative tool which aims to determine the PMI value by accounting for the raw material inputs based on the bulk API output	(Diorazio et al., 2021)
Convergent PMI calculator	Analytical – Quantitative	Quantitative tool which aims to determine the PMI, but allows multiple branches for single step or convergent synthesis	(Diorazio et al., 2021)
MedChem Tips and Tricks	Guidance – checklist	Qualitative checklist covering purification, solvent selection, reagents, energy, and resources	(ACS, 2016)

Innovation Scorecard Calculator	Analytical – semi-quantitative	Semi-quantitative tool using a statistical analysis of 64 bulk active pharmaceutical manufacturing processes encompassing 703 steps across 12 companies to provide a relative process greenness score	(Roschangar et al., 2018)

Despite the effort to develop tools and guidance to integrate environment, one limit of the Green chemistry approach is the lack of Lifecycle perspective. It usually considers the gate-to-gate perspective. We can also mention the lack of deepness of some tools. For instance, the PMI indicator is based on the weight of waste, it does not consider neither the treatment nor the composition. In other words, with this indicator, 1 kg of mercury will contribute the same than 1 kg of wastewater in the PMI perspective.

- *International Society for Pharmaceutical Engineering (ISPE) sustainability perspective*

The ISPE is defining itself as a *"nonprofit association serving its members by leading scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle".* They are providing guidelines in several topics, based on working groups of the pharmaceutical industry stakeholders, to share the best practices and knowledge in place.

In 2015, the ISPE has published a Sustainability handbook (ISPE, 2015). Even if LCA is mentioned several times in the handbook, it is built around the aspects below:

- *Energy*
- *Process development and Bulk Drug Products Manufacture*
- *Formulation and Packaged Drug Products Manufacture (non-exhaustively)*
- *Formulation and Packaged Drug Product Manufacture and Logistics (non-exhaustively)*
- *Pharmaceutical and Biopharmaceutical Manufacturing Supply Chain*
- *Site and Facility Design Considerations*
- *Heat Ventilation Air Conditioning (HVAC) systems*
- *Electricity*
- *Utilities*
- *Waste management*

From those aspects, we can understand that this handbook is focused on a gate-to-gate perspective, with recommendation for processes and infrastructure.

- *Environmental Risk Assessment (ERA)*

The Environmental Risk Assessment (ERA) can be define as *"process for evaluating how likely it is that the environment may be impacted as a result of exposure to one or more environmental stressors, such as chemicals, disease, invasive species, and climate change."* (McIntosh and Pontius, 2017). However, in the pharmaceutical context, the ERA refer to a specific assessment related to the eco-toxicity of the APIs. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the US are preconizing methods to perform such studies.

  - *European ERA*

A guideline to perform ERA was made available by the European Commission in 2006 (EMEA, 2006). The methodology recommended is in four phases, as described in the figure 36.

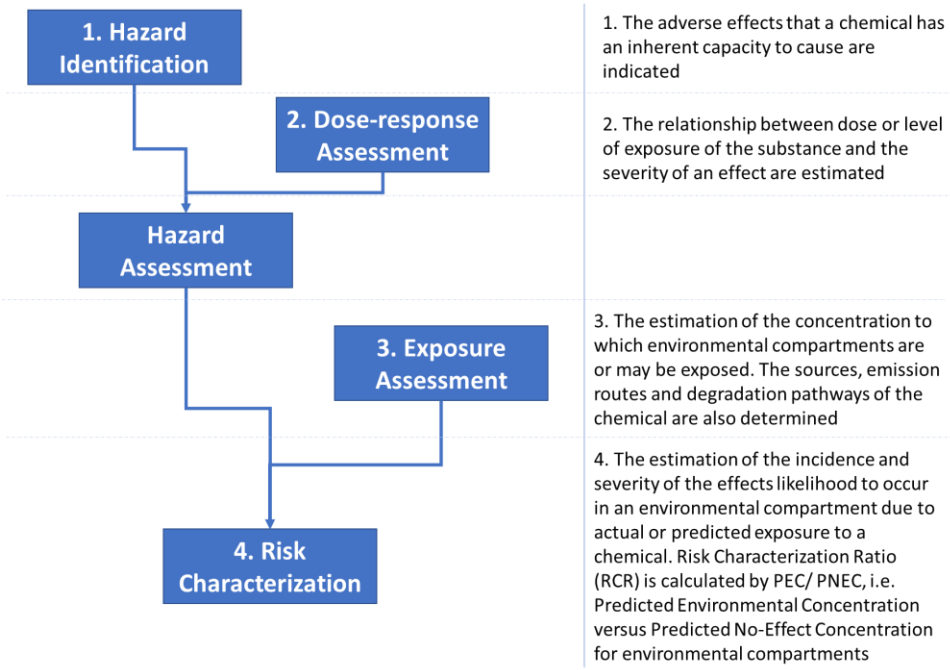


Figure 36 - Steps of an European ERA, adapted from Manuilova (Manuilova, 2003)

As stated by Manuilova (Manuilova, 2003), the main philosophy of this assessment is to evaluate the Predicted Environmental Concentration (PEC) / Predicted No-Effect Concentration (PNEC) ratio. The tests aimed to identify also other environmental parameters such as the potential bioaccumulation, the persistence in the environment. They can take the form on experimentations on zebrafish or daphnids. A principal limit is the fact that these tests are only focused on the API.

- *US Environmental Assessment (EA)*

In the US, the EA is based on three steps, Problem formulation, Analysis, and Risk characterization, as illustrated with the figure 37.

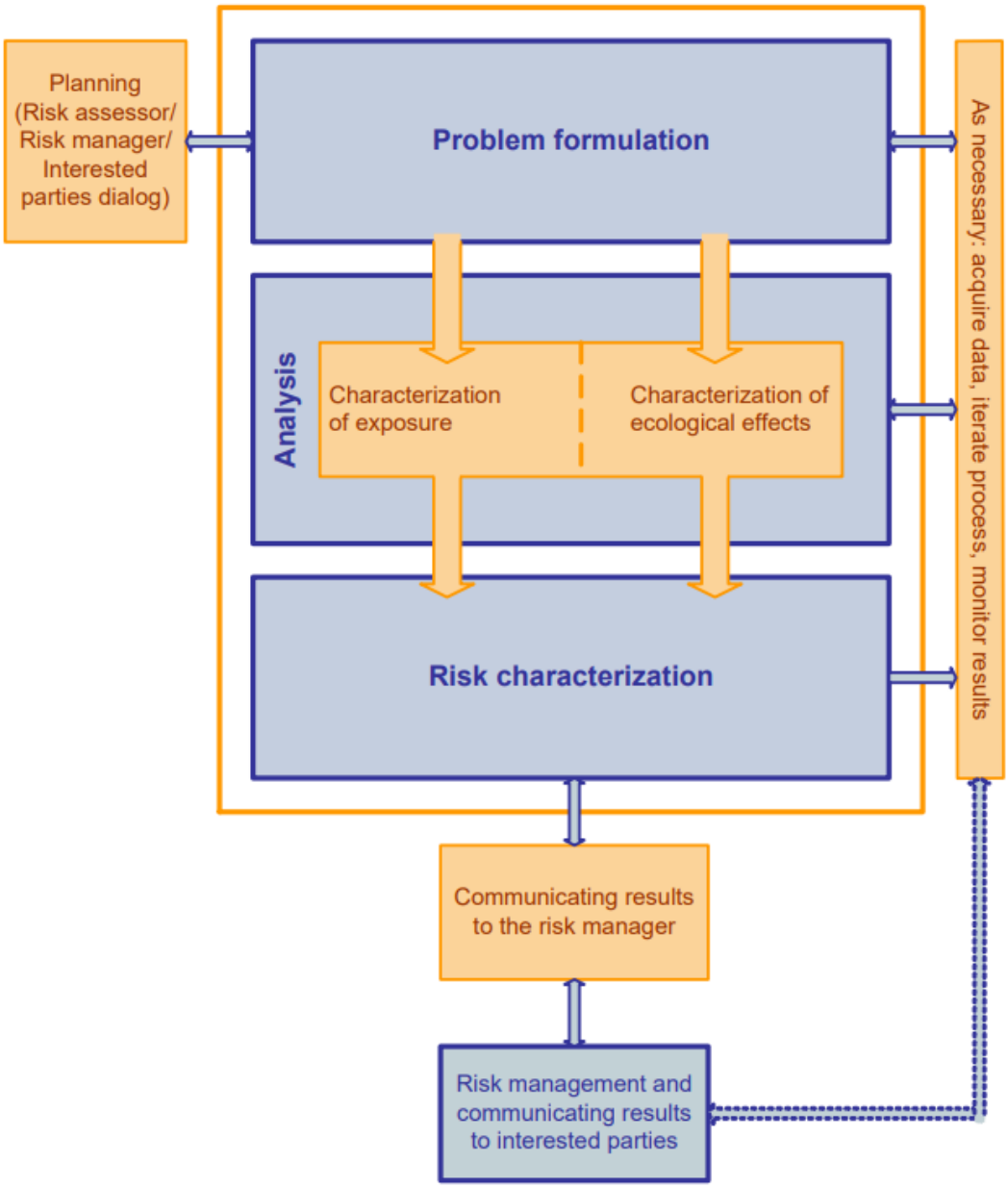


Figure 37 - The three steps of US EA, from Manuilova (Manuilova, 2003)

Like the European ERA, EA is determining PEC/PNEC ratio.

This table 30 is presenting a comparison of main aspects of the ERA and EA systems.

Table 30 - Comparison between EA (US) and ERA (EU), from Manuilova (Manuilova, 2003)

Category	EA (US)	ERA (EU)
Scope	1. The methodology is broad in scope, considers chemical and non-chemical stressors. 2. For predictive and retrospective assessments. 3. The methodology is not prescriptive due to its generality. The US method includes the EU method. However, the scope of the method is not unlimited. It does not discuss accidentally or deliberately introduced species, or genetically modified organisms.	1. The EU method is only intended for the assessment of chemicals. 2. Is intended for predictive studies. 3. Methodology is prescriptive due to its specificity (for example, more than 60

		equations are given in the guidance).
Data requirements	1. No minimum data set is defined in the guidance. 2. The credibility of the decisions is directly proportional to the quantity of representative data used in the analysis.	1. Minimum data requirement for exposure analysis: producers and importers are required to submit a specified data set, the so-called base-set.
Type of data	1. Collection and use of site-specific data is encouraged.	1. Use of standardized/default values as a first approach is preferred. This can lead to overly conservative estimates. The default values represent a worst-case scenario. Site specific data is needed to replace the default values.
Iteration	1. A new iteration is only required if previous iteration could not define the risk in a way to support the management decision.	1. Iteration is based on the result of the PEC/PNEC ratio. If the ratio is more than one, then iteration is recommended. 2. There is no recommendation to iterate if the ratio is less than 1. 3. The guidance gives elaborate testing strategies to implement if PEC/PNEC ratio is more than one.
Risk description and presentation	1. Risk(s) can be estimated and described by one or a combination of the following methods: • Single-point estimate: quotient method, • Stressor-response relationship curve, • Estimates incorporating variability in exposure or effects, • Process models.	1. Risk is described and presented as the PEC/PNEC ratio, which is the same as the U.S.EPA single-point method. This clearly limits the risk assessor to one simple method even if other methods would have been more appropriate.
Common points	1. Data gathering is the responsibility of chemical producers and importers. 2. Both support tiered approach to the risk assessment.	

- *Summary*

All these approaches are going in the direction of the Environmental burden reduction of medicines. However, it can be noted that they are all lacking both holistic perspective in terms of environmental indicators and Lifecycle perspective in terms of scope.

II.6 Summary of the state of the art

To support the development of new products or service, the design science and engineering provide methods and tools since decades (Aoussat et al., 2000; Cooper, 2019; Lahonde et al., 2010; Pahl et al., 2007). In regards of the sustainability issues, the field of Design for Sustainability grow since 1990 (Ceschin and Gaziulusoy, 2016).

The Eco-design approach is one of them and focus on the Environmental sustainability, by integrating the environmental aspects into the design of product and service, in both holistic environmental perspective and lifecycle mindset. Methods and tools to implement such approach have been developed by the scientific community since 1990 (Schäfer and Löwer, 2021).

The pharmaceutical sector does not avoid the paradigm of each Human activity to generate pollutions. This sector has embraced some of these issues through the study of the eco-toxicity (Hignite and Azarnoff, 1977) of the APIs, the footprint of their own facilities (ISPE, 2015), and their processes (Anastas and Williamson, 1996).

However, the literature let us think that the pharmaceutical industry does not consider yet the environmental issues, both with holistic environmental indicators and lifecycle perspective, as in the figure 38.

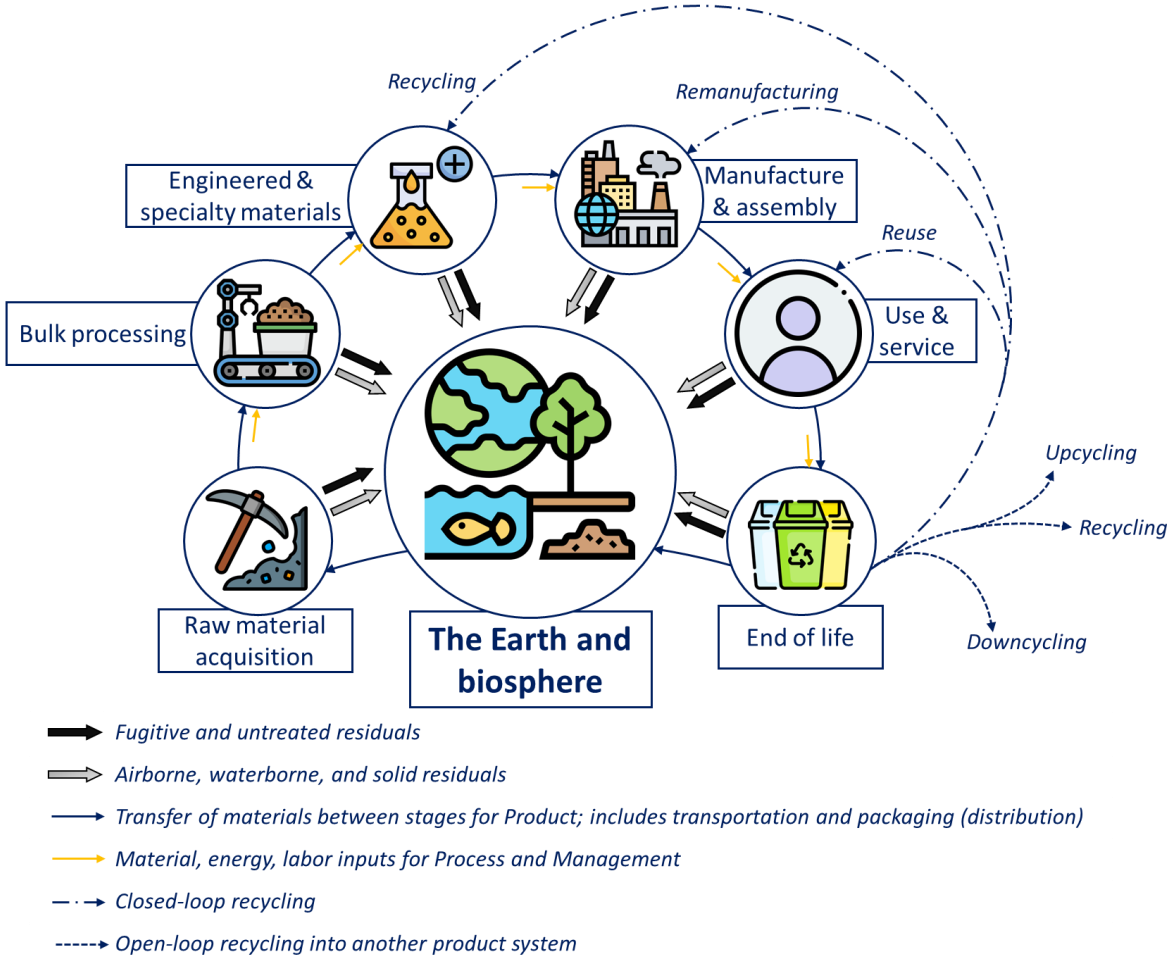


Figure 38 - Generic lifecycle of a product, with recycling loops, adapted from Keoleian (Keoleian and Menerey, 1994)

These observations allowed us to propose the problematic and the hypothesis linked to this research, which are described in the next chapter.

Phase 2

Chapter III

Problematic and hypothesis

« Savoir s'étonner à propos est le premier mouvement de l'esprit vers la découverte »
Pasteur, décembre 1983, Conférence de la société chimique de Paris
France culture, n.d. Pasteur, savant national

"Knowing how to wonder about is the first movement of the mind towards discovery"
Pasteur, December 1983, Paris Chemical Society Conference
France culture, n.d. Pasteur, savant national

III Problematic and hypothesis

Based on the context & related stakes of the work presented in chapter I, and in regard of the elements exposed in the chapter II, this chapter will present the research problem and the solution hypothesis.

III.1 Problematic statement

As mentioned in the chapters one & two, the Humanity is facing an environmental crisis which is linked to its way of living. The modern society needs to change its paradigm of production and consumption to decrease its environmental burden. This first observation led the scientific community to develop design approaches, which includes environmental perspectives in a holistic manner: the Eco-design. However, the industry seems to struggle to integrate the environmental sustainability into their decision making.

Methodologies and tools were made available by researchers to support the Eco-design approach. However, this mindset is not yet implemented in each industrial sector in a systemic way. It is particularly true within the pharmaceutical sector. Despite its effort to assess several environmental parameters of its products, such as the eco-toxicity, a lack of Eco-design approach is perceivable in the development process of medicine products.

The development process of a pharmaceutical product is a long journey where the efficacy and the safety for the patient are evaluated. The average time of this process is around 10 years and R&D practitioners are nowadays challenged to reduce this time. The environmental assessment can be time-consuming and, for an LCA, requires data which might not be available depending on the phase of the development process. Currently, environmental assessment through a holistic environmental view and lifecycle perspective is not performed during the medicine NPD. The third observation led us think that today, Eco-design levers are not clear within this NPD.

With these observations in mind and in order to foster the Eco-design practices, the works presented in this doctoral thesis manuscript are structured around the problematic below:

How to foster the Eco-design practices into the New Product Development of medicines in a systemic way?

This problematic can be decomposed to have a better understanding of the underlying concepts behind it.

The notion of ***"foster"*** refers to the fact that currently, environmental parameters are already studied. However, the lack of holistic environmental view and lifecycle perspective do not allow the pharmaceutical industry to state that they are Eco-designing products.

A second part is around ***"Eco-design practices"***. It refers to the need identified in the literature to provide development teams with tools and methods to be able to face this Eco-design journey.

The third part of the problematic, ***"into the New Product Development of medicines"*** refers to the process engaged to develop a new drug. The possibility to structure an Eco-design approach within the current NPD process is emphasized.

Finally, the notion of ***"systemic way"***. This notion highlights the necessity to structure the organization in order to be able to integrate environmental aspects into each layer of the decision making of the development of a medicine product.

III.2 Hypothesis identification

To answer this problematic, two axis of resolution who are complementary are adressed. They are based on the integration model of Brones, which was the spine of the work. The organizational axe and the operational one. The Macro level is intrinsically in the hand of the upper management of a company. Therefore, effort to build the research around the Meso, Micro, and Soft side levels, was made.

III.2.1 First hypothesis, organizational axe

As described in the literature, the identification of phases with decision making impacting the environmental footprint is key to ensure the success of an Eco-designed approach. Therefore, a first hypothesis, which is linked to both Meso and Soft side levels, can be formalized:

H.1: "An Eco-design approach can be structured within the current NPD of medicines product"

This first hypothesis can be addressed with sub-hypothesis.

The literature suggest that one of the key factor to a successful Eco-design integration is the inclusion of the stakeholders expectations in the development (Domingo et al., 2015; Keivanpour et al., 2014; Kota et al., 2013). The pharmaceutical industry is usually known to have a specific way of working, linked to ethic issues. For instance, this industry is not allowed to have direct contact with patients to not influence them with products that directly affect their health conditions. The complexity of the intrinsic functions of medicine products makes also singular the potential expectations of the users. Indeed, we can easily imagine that patient with a cancer will not consider the same way medicine that can cure them than healthy patient with a headache that want to relief their pain. It represents therefore a challenge that can be explored around the sub-hypothesis below.

H1.1: ***"It is possible to integrate the current environmental expectations of external stakeholders"***. This sub-hypothesis is questioning the identification of such stakeholders and their influence into the decision making of the medicine development. It contributes to the questions *"who?"* and *"what?"* to consider in the Eco-design journey; from the external stakeholder perspective.

Second key parameter highlighted to succeed the Eco-design journey in the literature, the necessity to integrate environmental aspects into the development process. Even if the pharmaceutical industry does integrate several environmental aspects during the development, both clear lifecycle perspective and holistic environmental footprint are missing. One strength of this industry is the regulation, which describe well the NPD process and the deliverable required for each step. However, research around the management of the pharmaceutical NPD process is not a recurrent topic in the literature (Romasanta et al., 2020). To study this topic, appear therefore relevant, especially to implement environmental aspects and the following sub-hypothesis is proposed: H1.2: ***"It is possible to identify Eco-design levers all along the current NPD process, as well as Eco-designers".*** As the medicine NPD process is a long journey, this sub-hypothesis is questioning *"where?"* and *"when?"* to focus efforts in order to Eco-designed medicines products.

III.2.2 Second hypothesis, operational axe

The literature highlights the need to make available tools and methods to support the teams with the Eco-design approach, from an operational perspective. However, the pharmaceutical companies seem to struggle to implement this mindset into their practices. A second hypothesis can therefore be formalized to feed the Micro level.

H.2: "The adaptation of Eco-design tools can optimize the appropriation of the Eco-design approach in the pharmaceutical sector"

Like the first hypothesis, the second one can be segmented with sub-hypothesis:

Eco-design maturity model are available in the literature. However, the implementation of such concepts is not yet done within the industry. Faludi et al. emphasis the necessity to adapt the academic concepts to the industry in order to foster the Sustainable design (Faludi et al., 2020). The NPD process of medicine product is regulatory driven and Eco-design parameters are not part of its scope. Therefore, a first sub-hypothesis to the second main one is proposed: H2.1: ***"It is possible to***

formalize an Eco-design maturity model for the pharmaceutical sector". The evolution of Eco-design practices should be tracked and supported. The formalization of such maturity model represents a tool who contributes to the questions *"when?"* and *"how?"*. By being at the frontier of the Meso level and the Micro one, this sub-hypothesis contributes to explore the interconnection of those two levels.

The environmental assessments are a key step to Eco-design. LCAs are considered today as one of the most relevant ways to perform environmental assessment in a holistic perspective. However, and as described by Emara, the appropriation of such tool is not yet well done by the pharmaceutical companies. One challenge is the complexity of its products, such as the complex raw materials, the heavy infrastructures to support the manufacturing, and the wide supply chain. The Product Category Rules (PCR) are important document that can help to structure the LCAs of products. Nowadays, no PCR are covering the complexities of all medicine products. In order to explore the development feasibility of such documentation, the following sub-hypothesis is proposed: H2.2: ***"It is possible to set LCAs guidance for specific pharmaceutical product types"***. This hypothesis feed the question *"how?"* of the global Eco-design journey.

III.3 Structure and methodological approach

As described by Brones, the Meso and Micro levels are interconnected. The Soft side is transversal and therefore, intervene in all layers of the Eco-design integration. The hypotheses are going in those directions and the sub-hypotheses are contributing to answer the related hypotheses.

It appears key for us to be able to answer several basic questions such as *"who?", "what?", "where?", "when?", or "how?",* to foster the Eco-design integration. The figure 39 formalizes the hypotheses within the adapted framework of Brones.

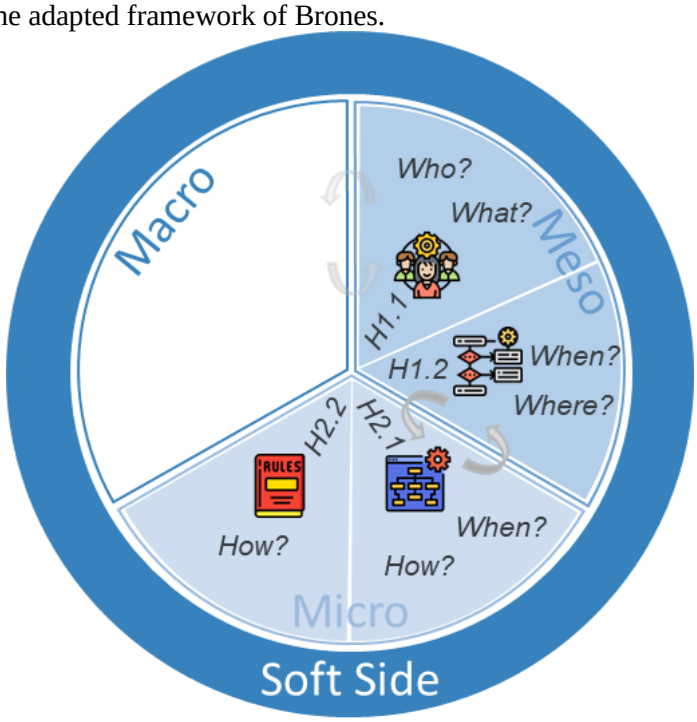


Figure 39 - Summary of the relation between the hypotheses / sub-hypotheses and the model of Brones (Brones and Monteiro de Carvalho, 2015)

To support the hypothesis formalized, each sub-hypothesis was considered as a piece to explore itself. The next chapters are structured with this mindset, by describing each independent experimentation with results who contributes to feed the research for the respective aspect explored.

III.4 Summary of chapter 3

From the observations of the state of the art presented in chapter two and the general context of chapter one, the problematic and the hypothesis conducted during this research were formalized.

The work focus on "***How to foster the Eco-design practices into the New Product Development of medicines in a systemic way?"***.

The manuscript addresses this broad question by addressing the problematic from an organizational perspective, by emphasizing that **"an Eco-design approach can be structured within the current NPD of medicines product"** (hypothesis one). A second dimension proposed around an operational perspective was formalized with **"the adaptation of Eco-design tools can optimize the appropriation of the Eco-design approach in the pharmaceutical sector"** (hypothesis two).

Through the sub-hypothesis, arguments that provide answers regarding these hypotheses were proposed. The next chapters are structured in order to highlight the approaches performed during the research to feed each sub-hypothesis. In that sense, the chapter four will present the work regarding the stakeholders' management, contributing to the H1.1. The chapter five focus on the pharmaceutical design process, identifying Eco-design potential within it (H1.2). An Eco-design maturity model, adapted for the pharmaceutical industry is described in chapter six, build on the Design Research Methodology (H2.1). Chapter seven present guidance to perform a Life Cycle Assessment for a monoclonal antibody, based on studies performed during the research (H2.2).

This manuscript will then end by chapters eight and nine, respectively the contribution & limits, and the conclusion & perspectives of the overall work.

Phase 3

Chapter IV

Soft side approach – Stakeholders management

« Les médecins administrent des médicaments dont ils savent très peu, à des malades dont ils savent moins, pour guérir des maladies dont ils ne savent rien »
Voltaire

"Physicians administrate drugs of which they know very little, to patients of whom they know less, to cure diseases of which they know nothing"
Voltaire

IV Stakeholders' management

When it comes to the implementation of Eco-design, one of the key aspects is to have a comprehension of both the stakeholders needs and level of environmental understanding (Domingo et al., 2015). In this chapter, a focus on the external stakeholders of the pharmaceutical industry will be done. A first part will describe the context of the topic to then expose our approach with the method, the results and a discussion. The purpose of this part is to identify the external stakeholders of the pharmaceutical industry, relevant for an eco-design approach. It is structured as presented in the figure 40.

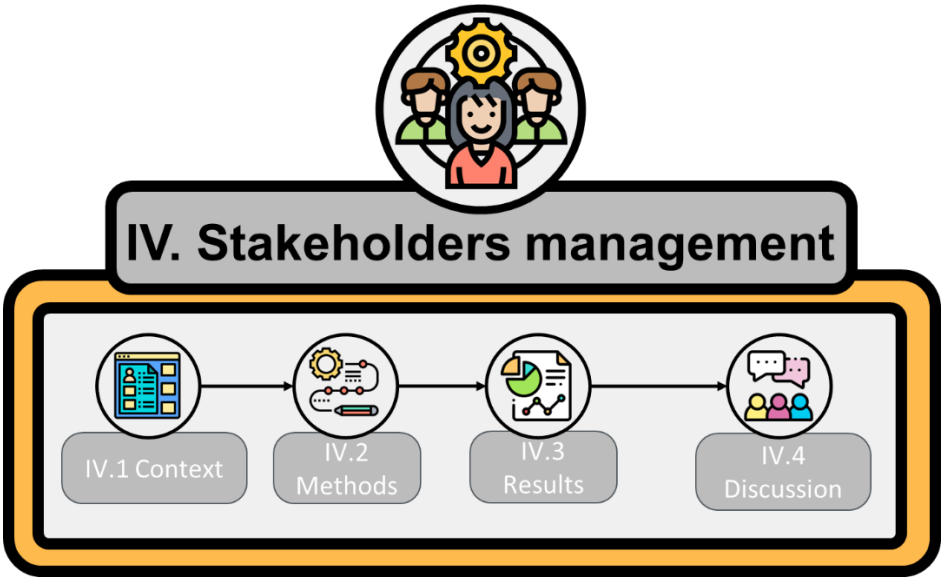


Figure 40 - Stakeholders management chapter structure

IV.1 Context

In this part, an introduction of the eco-design stakeholder's topic with general aspects, to then talk about the pharmaceutical ones, is proposed.

IV.1.1 General aspects

In his book, Freeman defined a stakeholder as *"any group or individual who can affect or is affected by the achievement of the organization's objectives"* (Freeman, 1984). The literature abounds of definitions and classification of it. For instance, Friedman and Miles have identified 75 definitions of stakeholders in their book . For those authors, they can be defined as *"groups of people with a distinguishable relationship with corporations".* They have split them into two categories, the strategic ones, and the normative.

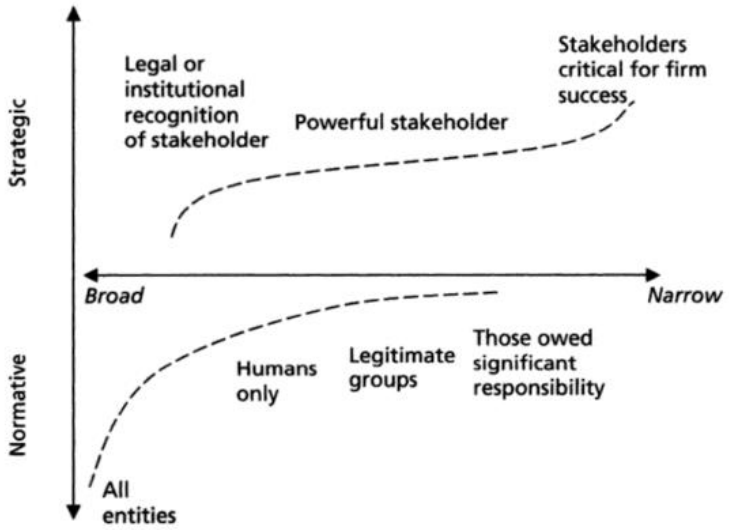


Figure 41 - Representation of strategic and normative dimensions of the stakeholders, from Friedman and Miles (Friedman and Miles, 2006)

To illustrate more the diversity of stakeholders' framework, I had a look on seven ones, available on the literature treating diverse topics (Domegan et al., 2019; Freeman, 2004; Ginige et al., 2018; Hall and Martin, 2005; Maj, 2015; Tcvetkov, 2022; Wheeler and Sillanpää, 1998). The point was not to propose an exhaustive view of stakeholders to consider, but rather to highlight the similar aspects between each framework. Table 31 summarize the harmonized stakeholders of the different papers assessed. The complete list of the original names of stakeholders and the correspondence with the harmonized list is presented in appendix 4.

Table 31 - List of the harmonized stakeholders proposed by the authors, based on the seven papers assessed

Harmonized Stakeholder	Description
Academia	Universities, or research organizations, engaged in research
Community	Individuals and groups that has direct interest in diverse topics which can put pressure
Consumers	Individuals and groups who uses goods and / or services
Customer	Individuals and groups who purchases goods and / or services
Financial	Individuals or groups engaged in financial flow
Industry	Private organization who is providing goods and / or services through the processing of raw material and manufacturing
Investor	Individuals or groups providing money in an entity with the expectation to make profit
Media	Organization who is providing mass communication
NGO	Non-Governmental Organizations that are engaged in diverse topics which can put pressure

Public authority	Public organizations that are involved in policy making, regulations, laws and rules
Societal group	Groups that are engaged in diverse topics which can put pressure

In the innovation management field, Geels has proposed a representation of social groups which he consider as relevant in the "modern western societies" (Geels, 2006). We can observe that the harmonized stakeholders identified above can feed the six families of stakeholders proposed by Geels as illustrated in the figure 42.

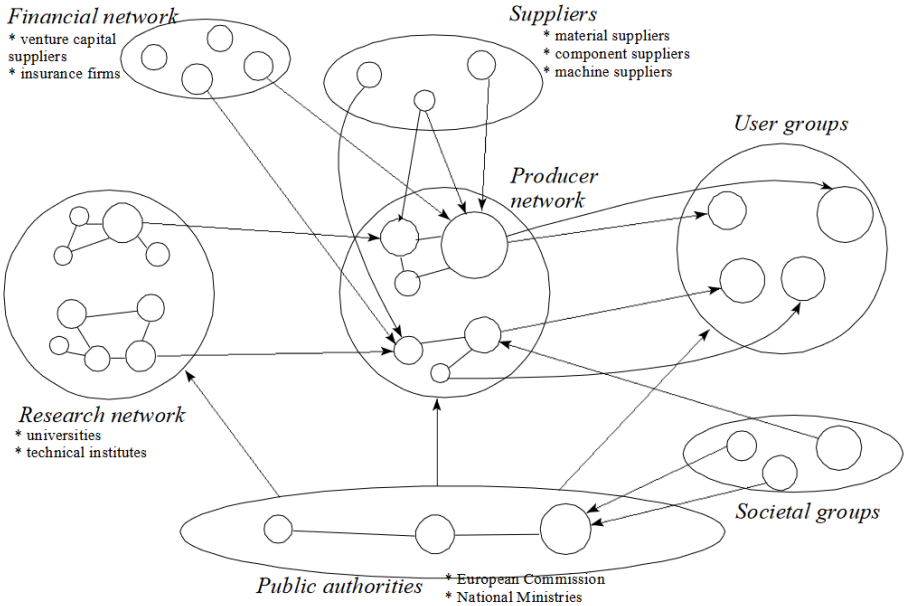


Figure 42 - Relevant social groups framework for the management of innovation, from Geels (Geels, 2006)

A similar framework was proposed by Brezet and Van Hemel and adapted by Tyl et al for the eco-design field, as shown in the figure below. The original authors proposed a framework based on stakeholders either internal to the company, in the value chain or in the extended value chain.

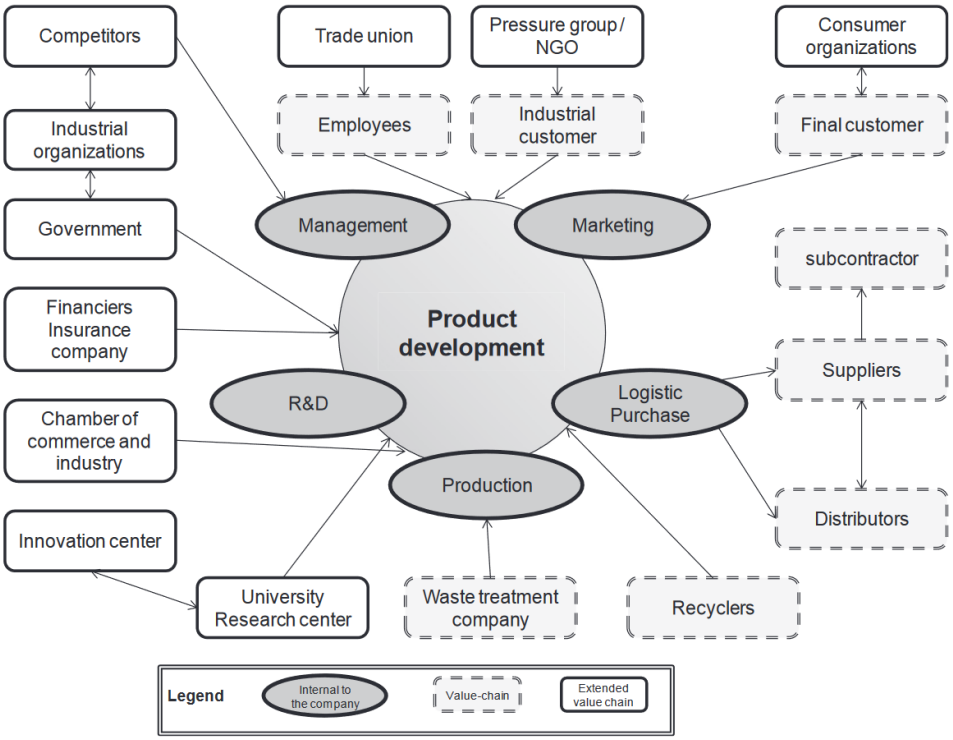


Figure 43 - Stakeholders in eco-design adapted from Brezet and Van Hemel, by Tyl et al (Tyl et al., 2015)

Tyl et al. have described in the eco-innovation topic that the inclusion of stakeholders may lead to tensions (Tyl et al., 2015). Nevertheless, the integration of their needs and expectations are keys in eco-design (Ferrón Vilchez et al., 2017; Torelli et al., 2019). Liu et al. have shown the positive influence of regulations, stakeholders' norms, and managerial mindset in the environmental considerations by firms (Liu et al., 2015).

Despite these facts, the identification of stakeholders and the considerations of their needs in terms of environmental dimensions remains a topic to explore (Egenhofer et al., 2018; Uribe et al., 2018).

IV.1.2 Eco-design stakeholders' management

A semi-systematic review (Snyder, 2019) was performed, including Eco-design, environmental practices, and related fields, in order to have an overview of the current trends of Eco-design stakeholders' framework. Through this approach, main stakeholders' groups in the Eco-design and environmental practices fields are highlighted.

Eight frameworks (Azapagic, 2003; Delmas and Toffel, 2004; Ferrón Vilchez et al., 2017; Jakhar et al., 2020; Salvioni and Almici, 2020; Silva et al., 2019; Tyl et al., 2015; Vallet et al., 2014) were assessed in this part and the table 32 summarize the harmonized stakeholders that can be identified. The complete list of the original names of the stakeholders and the correspondence with the harmonized list is presented in appendix 4.

Table 32 - List of the harmonized Eco-design stakeholders proposed by the authors, based on the eight papers assessed

Harmonized Stakeholder	Description
Academia	Universities, or research organizations, engaged in research
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Consumers	Individuals and groups who uses goods and / or services
Customer	Individuals and groups who purchases goods and / or services
Financial	Individuals or groups engaged in financial flow
Industry	Private organization who is providing goods and / or services through the processing of raw material and manufacturing
Investor	Individuals or groups providing money in an entity with the expectation to make profit
Media	Organization who is providing mass communication
NGO	Non-Governmental Organizations that are engaged in diverse topics which can put pressure
Public authority	Public organizations that are involved in policy making, regulations, laws and rules
R&D	Individual researcher or research group
Societal group	Groups that are engaged in diverse topics which can put pressure
Supplier	Organization or organization that provides goods or services to an industrial
Trade association	Groups of industries with a common interest that foster specific topics

IV.1.3 Summary of the theoretical background

The stakeholders management is a topic looked in many fields of research (Friedman and Miles, 2006; McGrath and Whitty, 2017; Savage et al., 1991; Uribe et al., 2018). It can be assumed that details of each framework will depend on both the topic & the scope investigated. Nevertheless, main families of stakeholders between generic models and Eco-design ones are similar, fitting also the framework proposed by Geels (2006).

IV.2 Methods

To address the research question of this chapter, an approach in two steps is proposed. The first is based on a theoretical approach and the second one an experiment with internal stakeholders of an international pharmaceutical company. Two of them are described in this part and main pros & cons are summarized in the table 33.

Table 33 - Main pro & cons of the theoretical framework and the experimental one

Approach	Pros	Cons
Theoretical framework	• Based on literature • Comparison with frameworks of other fields • "Neutral" approach	• Basic knowledge required • Rely on understanding of a pharma external stakeholder non expert • Theoretical framework

Experimental framework	• Based on stakeholders' experts • Space for participants to intervene • Dynamic	• Basic knowledge required • Rely on understanding of non-Eco-design experts • Language barriers • Preparation time consuming

The theoretical approach is based on a literature review. The experimentation was involving experts of the pharmaceutical stakeholders, but with no environmental knowledge. In that sense, it represents a complementary approach to be able to confirm the convergence point.

IV.2.1 Pharmaceutical stakeholders' management and theoretical framework

The pharmaceutical industry is a complex sector, which can be explained by the technicity of its products (Luu et al., 2021), but also with the wide range of therapeutical and development possibilities (Kelly, 2010; Magner and Kim, 2017; Malerba and Orsenigo, 2015). As mentioned above, a generic assumption can be made with the fact that specific stakeholders could be identified. For instance, each therapeutical areas will probably have their own stakeholders. Nevertheless, this part aim to highlight main families, as shown previously, to set an overall framework as a baseline for an Eco-design stakeholders' framework for the pharmaceutical sector.

A semi-systematic literature review was performed to get an overall understanding of the pharmaceutical stakeholders' and their key interactions. An overall framework is proposed, based on the seven papers assessed. These papers were chosen to cover diverse countries or continent. Table 34 is summarizing the scope of the different papers within the assessment.

Table 34 - List of the papers in the scope of the assessment with their related geographic perimeter

Country / Continent	Reference
Africa	(Kamau et al., 2021)
Australia	(Ryan et al., 2021)
China	(Shao et al., 2015)
Europe	(Van Ginneken, 2010)
France	(Saesen et al., 2020)
Europe	(AVISE, 2019)
US	(Niles, 2011)

IV.2.2 Pharmaceutical stakeholders' current trends

The environmental consideration of medicine products, from stakeholders is not a new topic. Trace of papers evaluating the environmental impact of some Active Pharmaceutical Ingredient can be found in 1977 (Hignite and Azarnoff, 1977) and are still a topic of concern (Wilkinson et al., 2022).

An integrative review as defined by Snyder (2019) was performed to generate qualitative insights regarding the current trends of the pharmaceutical stakeholders' and their environmental considerations.

IV.2.3 Framework based on experiment

As a complementary approach, an experiment with internal stakeholders of an international pharmaceutical company was performed in parallel. The purpose of this approach was to identify the external stakeholders, to consider in an Eco-design approach, from the point of view of internal

stakeholders of a pharmaceutical company. A preliminary step of this experimentation was to identify what can be considered as relevant expert to involve to then launch the experimentation. Both steps are described below.

IV.2.4 Internal stakeholders' identification

As the aim was to define an Eco-design external stakeholder's framework, which are not linked directly with the manufacturing nor distribution, of the pharmaceutical sector, a preliminary step of internal stakeholders' identification, the ones who are in close contact with the main external stakeholders in their daily activities, was done. This step was based on both an integrative review and knowledge of the authors.

Internal stakeholders may include transversal ones such as the Health, Safety & Environment (HSE), the quality, the supply chain, or continuous improvement services (also called LEAN). Those stakeholders are usually supporting the manufacturing activity of a pharmaceutical company. The R&D can be composed of Regulatory Affairs, Clinical development, Sites management, the Chemistry, Manufacturing, and Controls (CMC), or Data sciences functions. A group can be identified with the specific aim to manage the relation with external stakeholders, such as CSR, Public affairs or Communication. Another group who manages a complementary side of the stakeholders is the Market Access. Global pricing, and Horizon scanning & early insights are usually part of this group. Some companies build transversal teams around a same therapeutic area. It is therefore possible to find all the functions mentioned above, regrouped to focus on rare blood disorders for instance.

As the aim was to identify external stakeholders, which are not linked directly with the manufacturing nor distribution, and their priority, the internal stakeholders relevant for the approach as follow were considered: CSR, Public affairs, Communication, Global pricing, and Horizon scanning & early insights.

IV.2.5 Experimentation

The experimentation took the form of a workshop organized and animated by three environmental experts. Main aspects of their profiles are presented in table 35.

Table 35 - List of the animators of the experimentation

Animator number	Position	Expertise	Country	Scope of missions
1	Environmental toxicology manager	16 years in pharmaceutical industry	France	International
2	Eco-design expert	Seven years in pharmaceutical industry including 3 years on Eco-design related projects	France	International
3	PhD student Eco-design	• Eight years in pharmaceutical industry, including three years as PhD student in Eco-design & one year as chemical technician in R&D • License degree in pharmaceutical development	France	International

The session took place July 10th, 2022, for one hour and half. The main content is described in the figure 44.

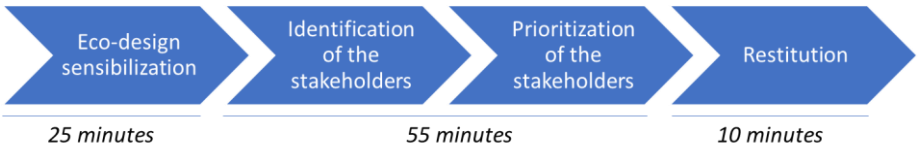


Figure 44 - Logic flow of the one hour and half session with internal stakeholders

Eco-design sensibilization: during this step, key definitions and concepts were displayed such as the definition of Eco-design (EEA, 2001), the Life Cycle Assessment approach (LCA) (EEA, 2017), or the Planetary boundaries framework(Persson et al., 2022; Rockström et al., 2009; Wang-Erlandsson et al., 2022). A LCA game was then proposed to go deeper in the sensibilization of the environmental aspects of a medicine product.

Through a digital board, participants had to consider what were the product Life Cycle stage when assessing the environmental impacts of a chemical-based medicine in tablet. Then, they had to estimate the environmental footprint contribution of each step, through three impact categories (Global warming, water scarcity footprint, and ecotoxicity, freshwater).

Then, the environmental targets of the companies were displayed, with a focus on the Eco-design ones. Ongoing actions of the company in terms of Eco-design were presented, alongside with a benchmark to finally end with some current trends.

Identification of stakeholders: based on the Geels framework, participants were invited to propose any external stakeholders that should be consulted or involved in an Eco-design approach.

Prioritization of stakeholders: the figure 45 is presenting the framework used for the prioritization of the stakeholders. Participants had to put the stakeholders identified regarding both their level of interest and power.

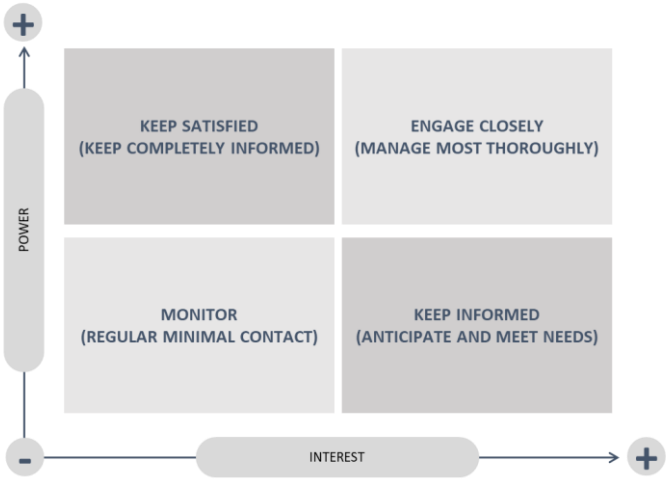


Figure 45 – Framework used for the prioritization

Restitution: ten minutes were kept at the end to summarize the overall results, get their feedbacks, and answer the remaining questions.

The participants were all employees of the same international pharmaceutical company, also the same than animator number one and two. They were chosen due to their position and the interaction with external stakeholders in their daily activity. Main characteristics of their profiles are described in the table 36.

Table 36 - List of participants of the experimentations with their main characteristics

Participant	Position	Expertise	Country	Scope of missions
1	Global Pricing Analytics & Innovation	12 years in the pharmaceutical industry, related to market access	France	International
2	Public Policy, Regulatory Policy	Nine years in regulatory policy, including three years in the pharmaceutical industry	France	International
3	Consumer Experiences & Insight	23 years in consumer insight, including seven years in the pharmaceutical industry	France	International
4	Rare Disease Product Manager	Eight years in the pharmaceutical industry	France	International
5	CSR manager	Nine years in media relations, including five years in the pharmaceutical industry	France	International

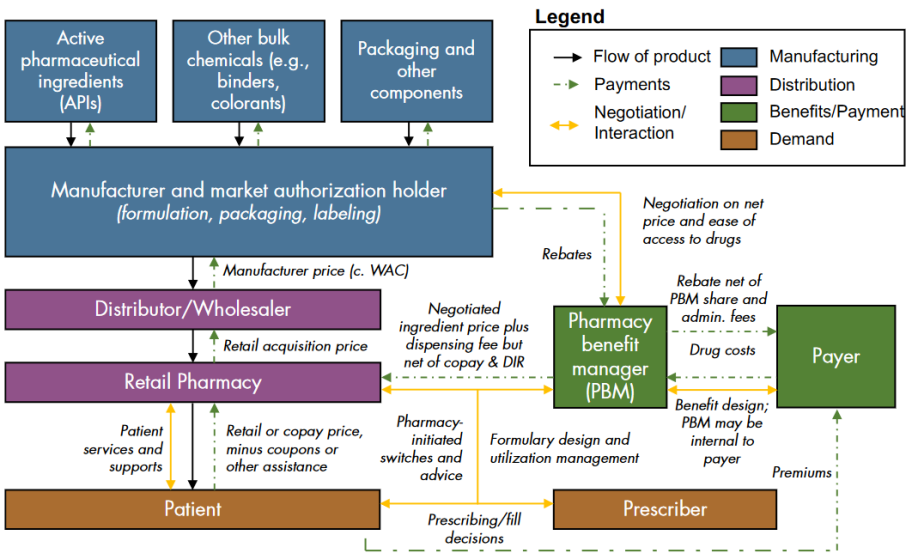
IV.3 Results

Qualitative results are described for both the theoretical framework and the one based on the experiment to then engage a discussion regarding limits, highlights, and convergence points.

IV.3.1 Pharmaceutical stakeholders' management and theoretical framework

To understand the stakeholders of the pharmaceutical industry, it is first needed to have a comprehension of the different interactions which are around a medicine product. As any manufactured product, drugs do not make an exception to the Life Cycle steps from raw material extraction / production, manufacturing, distribution (to wholesaler or pharmacy), use, to end-of-life (Luu et al., 2021). But before to be sold, product must be validated by the public authority of the country targeted.

Each country has their own specificities, especially regarding consumer and customer levels. Results of the literature review will be exposed here, by highlighting aspects for some countries to then set an overall theoretical framework. For prescribed drugs, it's usually healthcare professionals that will make the decision to choose a medicine from another, no matter the country. Additionally, the payment could be shared between insurance / patient / mutual, depending on the countries. The figure below illustrates the supply chain for brand-name drugs, dispensed through retail pharmacies (Mulcahy and Kareddy, 2021).



NOTES: c. = circa; DIR = direct and indirect remuneration; WAC = wholesale acquisition cost. Arrows denote relationships involving the flow of product (black arrows), information or negotiation (yellow arrows), and payments (green dashed arrows).

Figure 46 - supply chain for brand-name drugs, dispensed through retail pharmacies, from Mulcahy and Kareddy (2021)

- *France*

In France, the National agency of medicine safety (ANSM) give the market authorization. If the medicine does not require a reimbursement, it is directly commercialized. In the other case, the Health high authority (HAS) will evaluate both the medical benefit (SMR) and the improvement of the SMR (ASMR). This evaluation leads either to a negotiation of the price with the Economical committee of health products (CEPS) or to a final decision of a rate of reimbursement by the National union of insurance group (UNCAM). And just before the commercialization, a publication in the official journal is done.

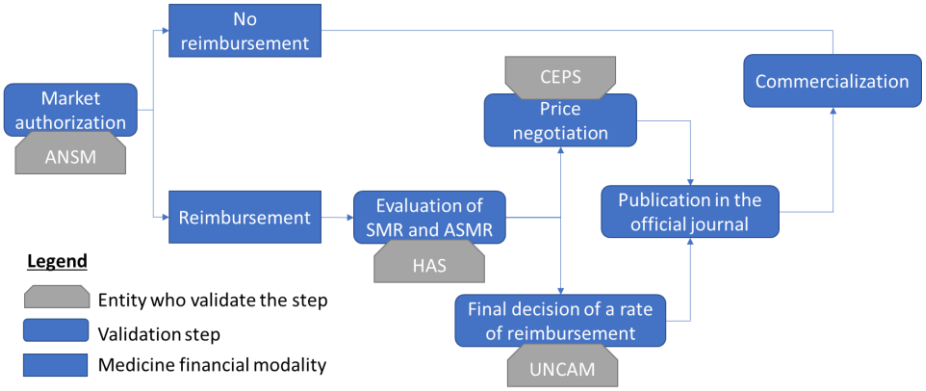


Figure 47 - French administrative process between the Market authorization to the commercialization with key entities involved, free translation from Safon and Suhard (2021)

A French association proposed in 2019 a mapping of health stakeholders for its national territory. The figure 48 is presenting this framework.

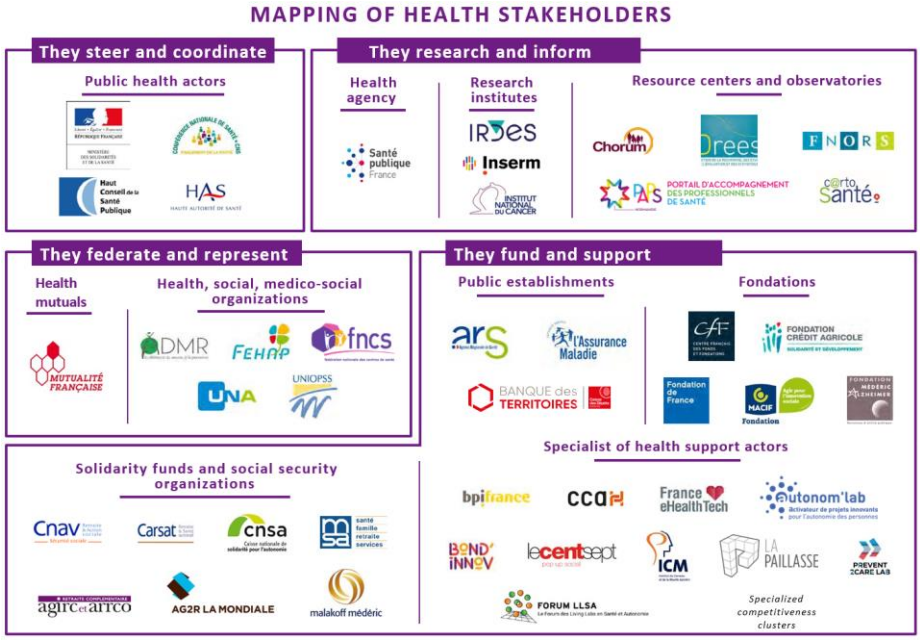


Figure 48 - Mapping of French health stakeholders, free translation from AVISE (AVISE, 2019)

- *Europe*

In their paper, Saesen et al. identified six groups of stakeholders: academic clinicians, patient organization, regulators, health technology assessment agency, payer, and pharmaceutical industry (Saesen et al., 2020).

More broadly, interconnection between the European Union and the member states cans be identified (Van Ginneken, 2010).

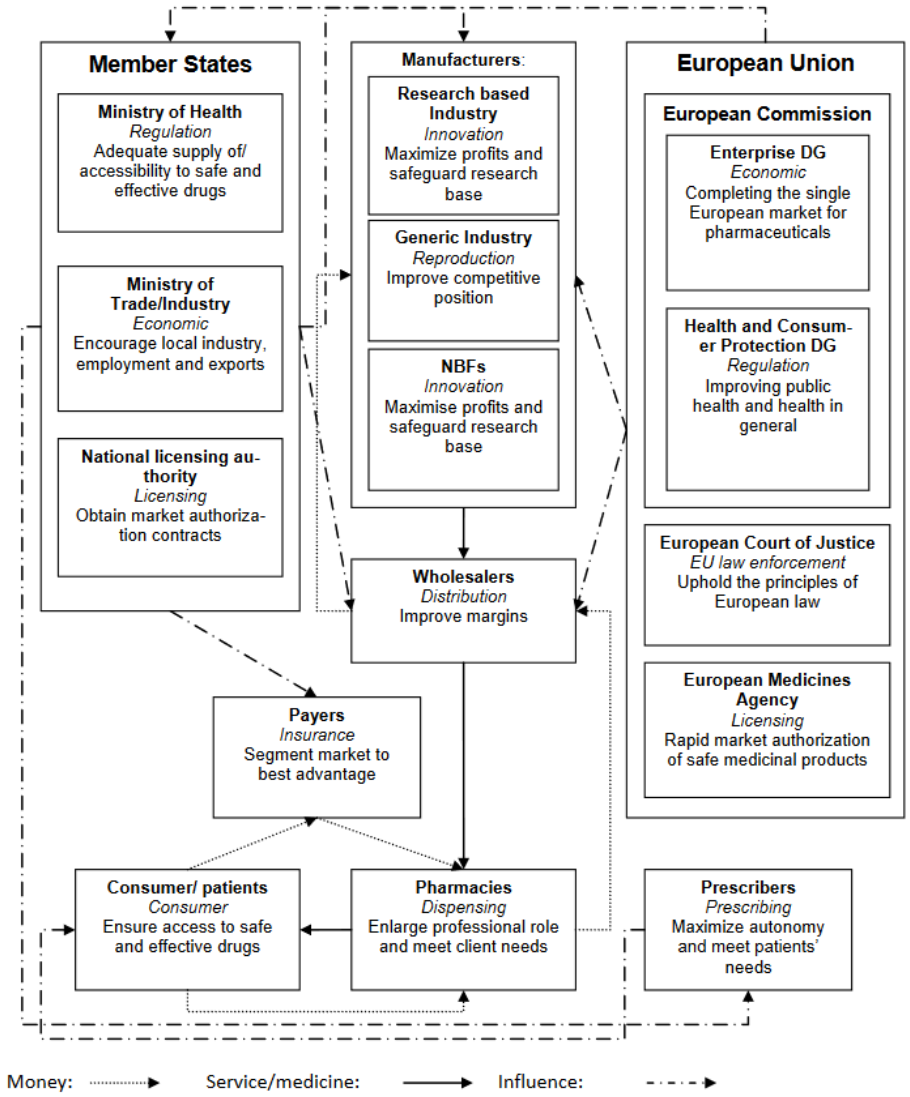


Figure 49 - Stakeholders in the European pharmaceutical market: functions and policy objectives from Van Ginneken (2010)

- *US*

In their research report, Mulcahy and Kareddy described families of stakeholders within circles. The main one includes Healthcare consumers and Health care providers. The second circle is defined with Healthcare facilities & Allied Health professionals, Pharmaceutical companies, Federal and State / Local health & Medicaid Medicare, and Diagnostic laboratories. The final circle is composed of Medica / Training facilities, Research associations, Professional associations & American medical association, and Accreditation organizations & the Joint commission (Mulcahy and Kareddy, 2021).

- *Australia*

Through a Delphi study, Ryan et al. identified a mapping of main stakeholders for diabetes prevention (Ryan et al., 2021). They segmented them in six groups, Policy makers & Politicians, Purchasers & Payers, Principal Investigators, Health Care Providers, Product Makers, and Patients & the public.

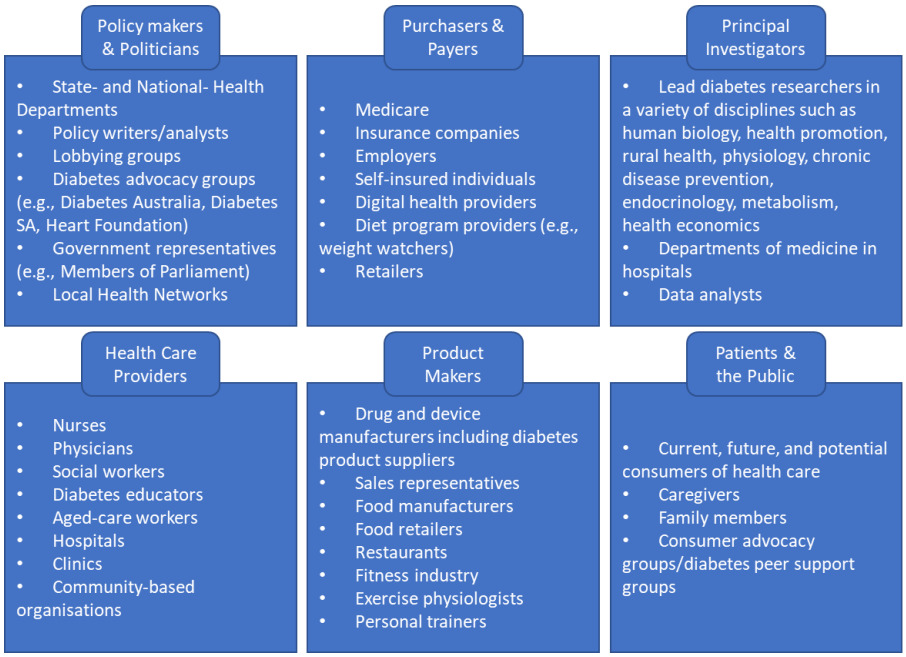


Figure 50 - Stakeholders mapping for diabetes prevention in Australia, from Ryan et al. (2021)

- *China*

A study performed by Shao et al. proposed a framework of stakeholders for essential drugs in China (Shao et al., 2015). Those products are defined par the World Health Organization (WHO) as drugs "that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be always available in functioning health systems, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford." (WHO, 2021).

By using the Delphi method, they were able to identify the Central government, the Provincial governments, the local governments, the Medical institutions, the Pharmaceutical manufacturers, the Delivery enterprises, the Patients, the Medical insurance institutions, the Mass media, the Community, and the Drug stores as relevant stakeholders.

- *Africa continent*

Another form of circle representation, Kamau et al. have defined five levels of stakeholders. The individual, the Interpersonal, the Organizational, the Community, and the Public policy (Wilkinson et al., 2022).

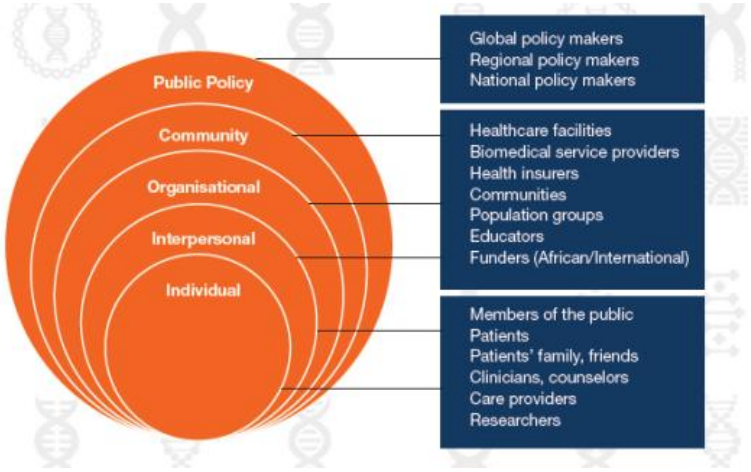


Figure 51 - The five levels of stakeholders in Africa continent, from Kamau et al. (2021)

- *Overall view*

With all the lists above, a stakeholder harmonized family list is proposed. The table 37 proposes a summary of it, based on the literature described above and the type of stakeholders who can fit within these families. The complete list of stakeholders identified with the related harmonized family is presented in appendix 4.

Table 37 - Numbers of type of stakeholders within each harmonized families per country or continent, based on the papers assessed

Reference	**(O'Riordan and Fairbrass, 2008)**	**(Kamau et al., 2021)**	**(Ryan et al., 2021)**	**(Shao et al., 2015)**	**(Van Ginneken, 2010)**	**(Saesen et al., 2020)**	**(AVISE, 2019)**	**(Niles, 2011)**
	International	Africa	Australia	China	Europe	Europe	France	US
Health care professional	None formalized	4	8	2	2	None formalized	None formalized	6
Patient & the public	1	4	4	1	1	1	None formalized	2
Pharmaceutical industry	1	None formalized	8	1	3	1	None formalized	1
Public authorities	1	3	6	3	7	1	8	1
Purchasers & Payers	None formalized	2	6	1	None formalized	2	1	1
Research		1	3	None formalized	1	1	3	1
Societal groups	1	2	None formalized	2	1	None formalized	31	2
Supplier	1	None formalized	None formalized	1	1	None formalized	None formalized	None formalized

For the purpose of the thesis, the definition as below of the different families of stakeholders will be considered:

Health care professional: basically, a healthcare professional (HCP), also known as healthcare provider, is a "licensed person or organization that provides healthcare services" (NIH, 2011). Various HCP can be identified. For instance, the National Institute of Health (NIH) is listing HCPs around Primary care, Nursing care, Drug therapy, and Specialty care (NIH, 2020).

Patient & public: patient include individual which is receiving healthcare product or service. The public can be defined as individuals in relation with the patients, without requiring any healthcare.

Pharmaceutical industry: private organization who is providing medicine products through the processing of raw material and manufacturing

Public authorities: public organizations that are involved in policy making, regulations, laws, and rules.

Purchasers & Payers: Organizations who are involved in financial and who contribute to the accessibility of medicine to patients

Research: individual researcher or research group involved in the development of new knowledge

Societal groups: Groups that are engaged in diverse topics which can put pressure and influence organizations

Supplier: Organization that provides goods or services to an industrial

The figure 52 presents the overall families of the healthcare products stakeholder's framework, with non-exhaustive examples.

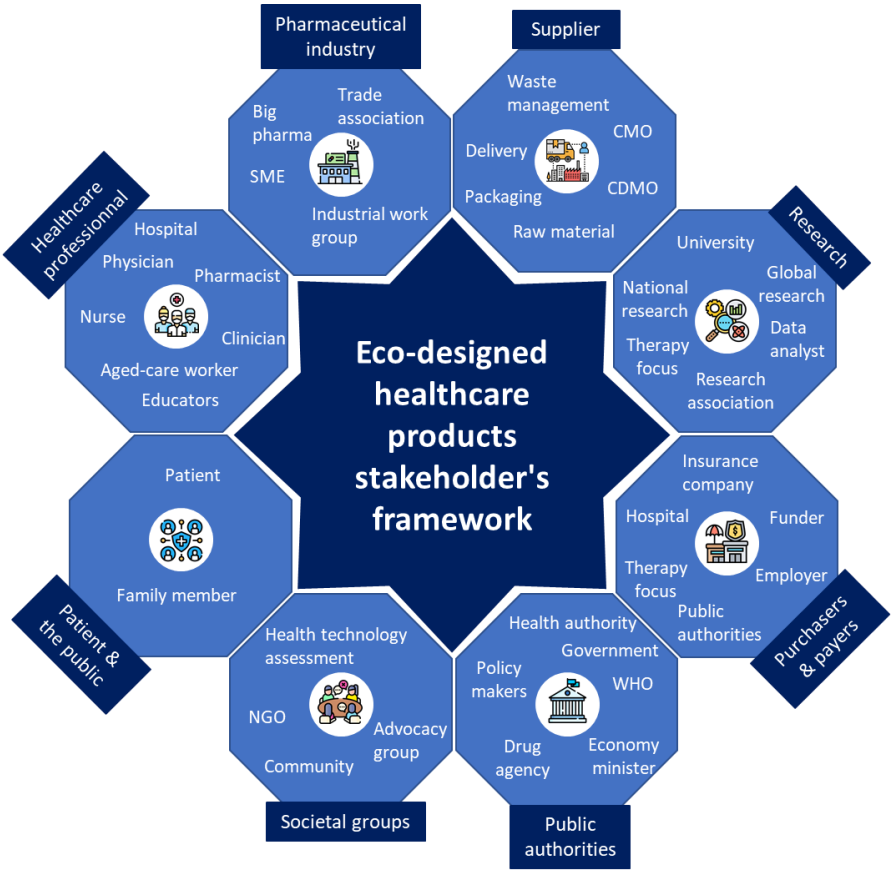


Figure 52 – Theoretical Eco-designed healthcare products stakeholders' framework

IV.3.2 Pharmaceutical stakeholders' current trends

In this part, examples who are showing trends regarding the environmental perception between the medicine products & environment from some stakeholders will be focused.

- *Healthcare professionals (HCP)*

The primary objective of HCP is to provide healthcare to the patient. The prevention of pollution was not a main element. Nevertheless, Dupont and Faure showed a switch of Mindset. The

study illustrates the willingness to include more environmental aspects into prescription by French interns.

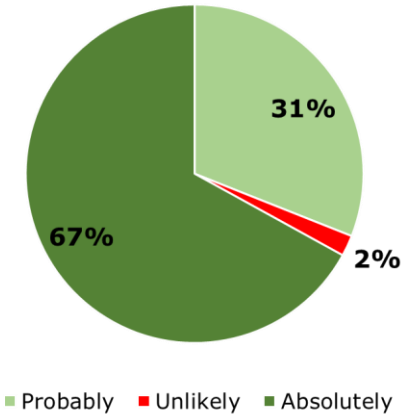


Figure 53 - Willingness to modify prescriptions with equivalent tolerance and efficacy, based on 117 French Medical interns, adapted from Dupont and Faure (2020)

Another output of the study showed that 85% of the survey participants are interested to be trained in the understanding of the ecological impact of drugs.

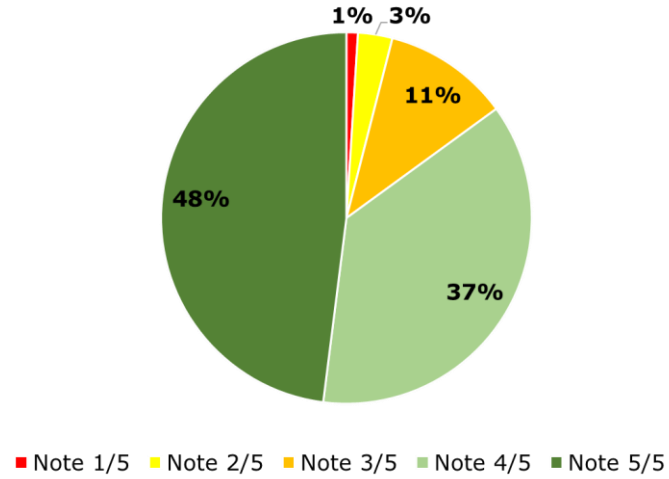


Figure 54 - Interest in training on the ecological impact of drugs, based on 117 French Medical interns, adapted from Dupont and Faure (2020)

Those figures highlight the lack of knowledge from HCP regarding environmental issues and the interest they have to be provided with proper information.

- *Pharmaceutical industry*

In this manuscript, the "pharmaceutical industry" as entities or organization who aim to provide medicine products will be considered.

The integration of environmental aspects into the pharmaceutical industry is not a new topic (Anastas and Williamson, 1996; Hignite and Azarnoff, 1977) but was mainly focused on a Cradle-to-gate perspective (Azuma et al., 2016; Carlsson et al., 2009; Larsson et al., 2007). Nevertheless, we can observe a change of paradigm, by the integration of the Life cycle perspective (Budzinski et al., 2022; Emara et al., 2018; Klemeš et al., 2021; Whitford et al., 2019). I performed in 2021 an assessment of public statement of 20 pharmaceutical companies. D data available in internet such as web page, 2020 annual report were used. The list of companies in the scope and the details of the assessment are presented in appendix 5. As a summary, three companies had specific eco-design targets for the whole products & in a life cycle perspective. Four of them had on packaging and 11

claimed to, either work in a life cycle perspective or to have performed LCA. Finally, 11 companies did not have any eco-design targets.

In other words, the pharmaceutical sector did not embrace at that time the eco-design at a global level. Moreover, some companies were mentioning working on "sustainability" but were in fact deploying green chemistry principles.

Demir and Min performed an assessment of Corporate Social Responsibility (CSR) reports of pharmaceutical companies (Demir and Min, 2019). They highlighted the level of maturity in terms of communication of the companies but also the weakness of some topics such as the supply chain.

All these elements show that the pharmaceutical industry is willing to embrace the environmental journey but is not yet including it in a full life cycle perspective.

- *Public authorities*

A first example of public authority can be from the National Health Service (NHS) of England. On July 1st, 2022, the NHS has published its "Delivering a Net Zero National Health Service" report (NHS, 2022). Focused on GHG emissions, the purpose of this report is to set strategy to reach what they define as "Net zero" direct emissions by 2040 and 2045 for indirect ones. The figure below illustrates what the NHS is including it its scope, showing the level of maturity of its carbon emission footprint.

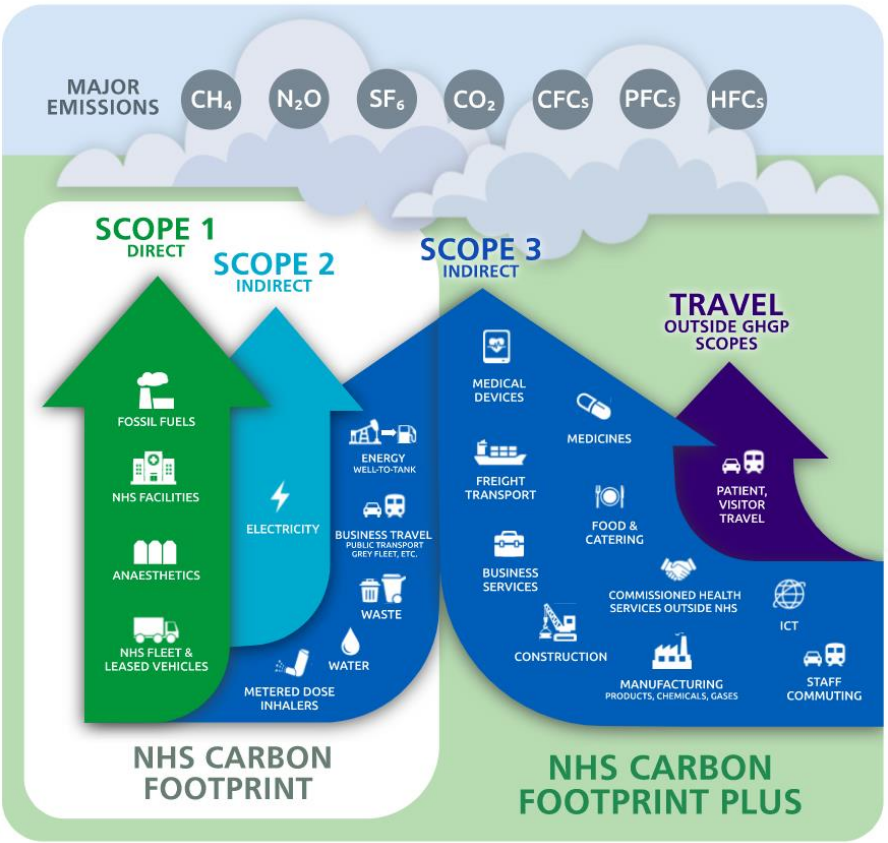


Figure 55 - Greenhouse Gas Protocol scopes of the NHS (NHS, 2022)

As shown in the figure above, medicines products, metered dose inhalers and other medical medical devices are included in the scope of their work.

The 11th of December 2019, the European Commission presented the European Green Deal (European Commission, 2019). It consists of a roadmap for the European Union to reach a sustainable economy. A mention of the pharmaceutical industry is made on the pilar "a zero-pollution ambition for a toxic-free environment" pilar, illustrated in the figure below.

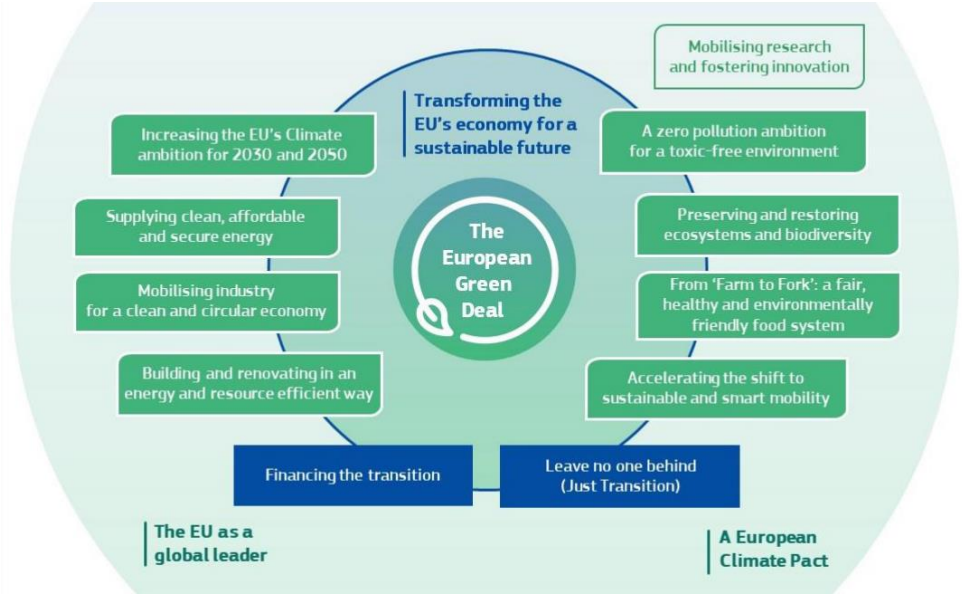


Figure 56 - Illustration of the European Green Deal, from the European Commission (European Commission, 2019)

On November 25th, 2020, the Pharmaceutical Strategy for Europe was adopted, in line with the European Green Deal (European Commission, 2020a).

Still linked to the European Green Deal, the Platform on Sustainable Finance made a call for feedback to build recommendations for technical screening criteria for the EU taxonomy the 3rd of August 2021 (Platform on Sustainable Finance, 2022). This taxonomy aims to support the European Green Deal by defining a "classification system for sustainable economic activities" (Platform on Sustainable Finance, 2021a). In the Annex, a chapter is dedicated to the manufacture of basic pharmaceutical products and another one for basic pharmaceutical preparations (Platform on Sustainable Finance, 2021b).

A more global approach was proposed by the European commission to push the integration of environmental aspects into design. The Eco-design for Sustainable Products Regulation aim to ensure that companies develop eco-designed products by 2030, with both a sustainable and circular mindset.

Figure 57 - Overview of initiatives in the Circular Economy package, from European commission (European Commission, 2022)

- *Societal groups*

In France, a think tank organized to foster an economy without carbon generate guidance, specific to activities for their decarbonation (The Shift Project, 2022). In November 2021, they published a report by proposing figures and guidance for the decarbonization of the French healthcare system (The Shift Project, 2021). In their calculation, they have estimated the purchase of medicine as the main contributor to the carbon emission (33%), and at the second place, the purchase of medical devices (21%).

International Non-governmental organization (NGO) which is present in several countries, "Health Care Without Arm" is defining itself as an organization who helps to "Transform health care worldwide so that it reduces its environmental footprint, becomes a community anchor for sustainability and a leader in the global movement for environmental health and justice" (Health Care Without Harm, 2013a). They are structured around six programs, to support the health systems in the environmental journey: Global green and healthy hospitals, Climate change and health, Sustainable procurement, Health care waste, Mercury in health care, and Safer chemicals (Health Care Without Harm, 2013b).

A similar organization called "Practice Greenhealth" is proposing for the United States a network to foster "sustainable health care, - by - delivering environmental solutions to hospitals and health systems" (Practice Greenhealth, 2022a). They are proposing guidance around 12 topics: Buildings, Chemicals, Energy, Food, Sustainable Procurement, Transportation, Waste, Water, Climate & Health, Engaged Leadership, Greening The Operating Room, and Sustainability Program Fundamentals (Practice Greenhealth, 2022b).

The non-exhaustive elements presented above shows that, despite the singular role of medicine products to contribute to a healthcare system, stakeholders with power of influence are willing to integrate more the environmental aspects, related to those products, in their daily activities.

IV.3.3 Framework based on experiment

During the stakeholder identification phase, 25 different stakeholders were identified. Some of them were tagged in different families (e.g.: UN groups, identified within the Public authorities, the Societal groups, and the Users groups).

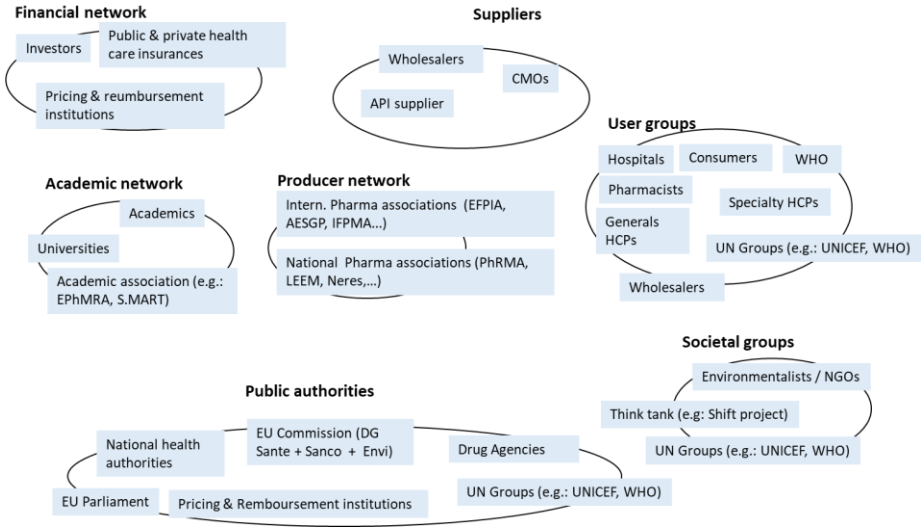


Figure 58 - List of stakeholders identified during the experimentation within Geels' framework

During the phase of prioritization, discrepancies appeared between participants and will be discussed in part IV.4.2.

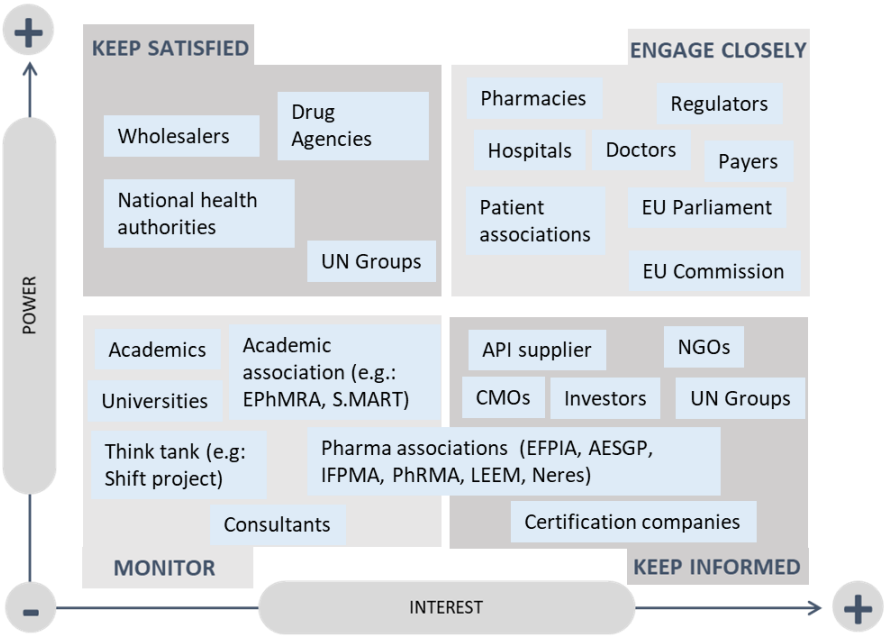


Figure 59 - Prioritization of stakeholders identified during the experimentation

IV.4 Discussion

In this part, major's highlights, convergence points and main limits are exposed.

IV.4.1 Framework based on theory

The theoretical framework proposed is constituted of eight families: the healthcare professionals, the patient & the public, the pharmaceutical industry, the public authorities, the purchasers & payers, the research, the societal groups, and the supplier. Similarities with generic frameworks can be highlighted, such as the need to consider legislators, government, consumer / patient, or NGOs.

Discrepancy can be noted regarding the media, which is usually present in generic frameworks but absent in the one for the pharmaceutical sector. It may represent a room of improvement, especially to foster the integration of Eco-design, by integrating the communication, with for instance the "influencers".

IV.4.2 Framework based on experiment

The focus of the experimentation was to identify external stakeholders, which are not linked directly with the manufacturing nor distribution, relevant to consider in the Eco-design journey.

Experts from a private multinational pharmaceutical company were involved to both identify and prioritize them. They were chosen linked to their daily activities, in relation with external stakeholders of the pharmaceutical sector.

General agreement within all participants was set to identify the stakeholders in the figure 58. However, discussion appeared to mention that specific ones could be defined in regards of therapeutic areas and geographic perimeters. Indeed, participants were mentioning for instance that, diabetes patient associations may not have the same perception of environment than other, especially due to the medicines available (e.g.: disposable insulin pens). The geographic scope was also mentioned as a key parameter, especially due to the different regulations, but also cultures.

Discrepancies between participants appeared during the prioritization, which can be explained by the difference of the scope of their missions. Some of the participants are working on Over the Counter (OTC) medicine, in other words nonprescriptive drugs, while some others are focused on

prescribed ones. This difference of scope leads to different considerations in the mapping of figure 59. For instance, as patient choose the medicine, patient associations have a strong influence and potentially high interest for OTC drugs. Meanwhile, an oncologic medicine is usually not decided by patient and has not the same benefit to the health condition of the patient. Therefore, patient associations should have both less power and interest on environmental aspects.

Main limit of the list is linked to the knowledge of the experts involved. Despite their background and the international scope of their missions, we can observe that many proposition are Europe centric. Another limit is the fact that experts of only one pharmaceutical company was involved. Even if they were representing different branch of this company, a bias from the culture and practices may be present.

IV.4.3 Major highlights and convergence points

Through the theorical approach, eight stakeholders' families relevant for healthcare products were identified. Some stakeholders were similar to generic frameworks (e.g.: public authorities) while some other were not part of it (e.g.: media).

The experimentation confirmed the theoretical framework and added a prioritization of stakeholders to consider. However, one of the qualitative outputs of this approach is the fact that frameworks could gain in deepness by adapting them regarding both therapeutic areas and geographic scopes, especially at national level.

IV.5 Summary of chapter 4

Drugs are nowadays considered as key products to ensure the wellness and well-being of populations, by preventing disease, cure them, attenuate symptoms or even diagnosis. But this societal contribution shall not blind the fact that medicine products present environmental impacts. By integrating the Environmental aspects into the design, Eco-design is an approach which can support industries to consider them. Even if some trace of Environmental approaches integrated into design can be found around 1960, 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 (e.g.: Green chemistry), the literature suggest that this sector seems to struggle when it comes to have a holistic approach of Eco-design.

A proper stakeholders management is described in the literature as one of the key factors to implement Eco-design. The paper aimed to identify relevant external stakeholders of the pharmaceutical industry to include, for the success of an Eco-design journey. To do so, an approach in two steps was performed. A first framework was build based on a semi-systematic literature review. In parallel, current trends of some of those stakeholders, regarding how they consider environmental aspects of medicine, were described. Then, a framework was built with experts from a multinational pharmaceutical company. A prioritization of stakeholders to consider was also generated.

Some specific stakeholders, due to the healthcare aspect, can be found (e.g.: healthcare professionals as customer, patients as consumer) and some stakeholders are less present (e.g.: media) than generic sectors. However, results show that main families of stakeholders of the pharmaceutical sector are similar to generic ones.

The experimentation confirmed the first theoretical approach and went deeper. Indeed, participants agreed on the identification of stakeholders. However, discrepancies appeared during the prioritization. Participants highlighted that first, differences should be made between OTC drugs and prescribed ones. Then, specific stakeholders could be identified regarding both geographic perimeters and therapeutic class areas. Even if stakeholders' families are similar, this segmentation may lead to different prioritization of external stakeholders.

After this exploration within the Soft side of Eco-design through the stakeholders' management, the next chapter will focus on the Meso level, and more specifically on the pharmaceutical design process.

Phase 3

Chapter V

Meso approach – pharmaceutical design process

« Blâmez le processus, pas les gens »
W. Edwards Deming

"Blame the process, not the people."
W. Edwards Deming

V Pharmaceutical design process

In the Eco-design perspective, it is key to support teams and activities who contribute, in their decision-making process, in the environmental footprint of the product. This chapter aim to understand where in the New Product Development (NPD) process of a pharmaceutical product Eco-design should be implemented; with the perspective to feed the hypothesis H.1.2: ***"It is possible to identify Eco-design levers all along the current NPD process, as well as Eco-designers".*** The Context of this part will be presented in V.1, with the material & methods of this research in V.2. Results, Discussion, and Conclusion of our research are then presented respectively in part V.3, V.4, and V.5. It is structured as presented in the figure 60.

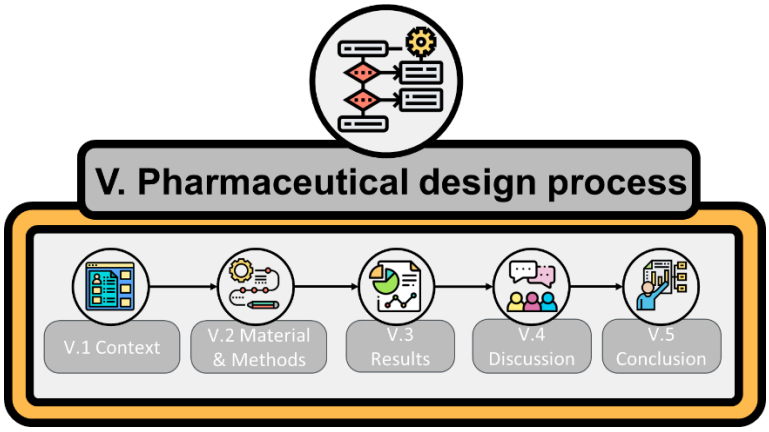


Figure 60 - Pharmaceutical design process chapter structure

V.1 Context

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. 59), the pharmaceutical development, the technology transfer, the commercial manufacturing, and the product discontinuation (ICH, 2008).

Even if Ramnarine et al. (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.

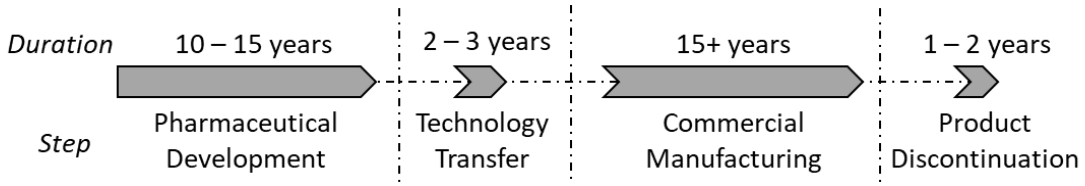


Figure 61 - Ramnarine Lifecycle steps of medicine, based on ICH guideline (ICH, 2008)

As the aim was to set a framework of eco-designers within the NPD of medicine product, the rest of the manuscript is focused 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. 60.

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 therapeutical 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 phase2b is the same as of phase2a 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.

After the first launch, the life of the product continues, often referred to as phase4. In phase4, 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. 59). 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. 60 except the LCM.

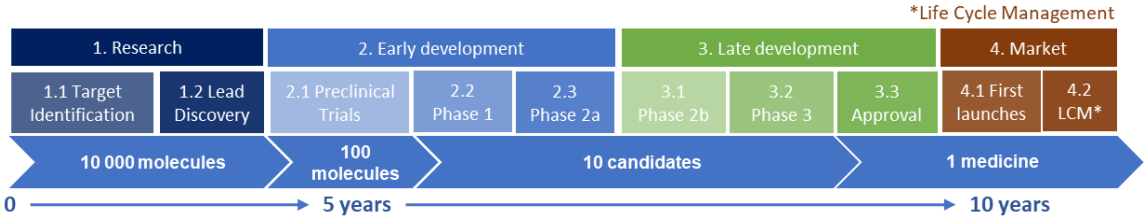


Figure 62 - Sub-steps of the pharmaceutical development of medicines to the LCM

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.

Emara, who performed a review of Life Cycle Assessment of this sector, available in the literature can be also mentioned. 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 (Alfonsi et al., 2008; Tucker, 2006), 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 (ICH, 2012). The holistic approach proposed by the eco-design seems therefore relevant to implement within this industry.

V.2 Material & method

This chapter 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. Main ones are summarized in the table 38, based on literature for the semi-structured interview, and on our perception for the assessment method.

Table 38 - 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

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.

V.2.1 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 39. 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 6 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 review was performed to correct the misinterpretation of the interviewer, which was not an expert of the pharmaceutical industry.

Table 39 - Main characteristic summary of the interviewees

Participant	Position, Expertise	Related years of expertise	Country	Environmental knowledge
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

The interviews were performed between January 12, and January 21, 2021. It lasted 45 minutes to one hour and a half, with an average of one hour.

To avoid biases linked to pharmaceutical knowledge-perception, the interviews were supported by an independent interviewer, holding 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.

V.2.2 Environmental aspects root cause within R&D decision making

The second experiment was based on a qualitative evaluation. Results of a Life Cycle Assessment (LCA) of an existing medicine were made available to an environmental expert of Sanofi. He 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, the details of the LCA results will not be displayed. 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 following table.

Table 40 - 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)*

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. 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 can be mentioned.

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 figure 63). The purpose of this step was to identify the deliverables with "eco-design potential". This notion was defined 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 7.

V.3 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.

V.3.1 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 figure 63.

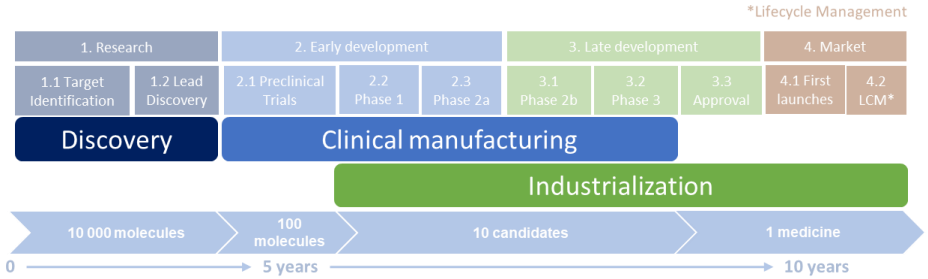


Figure 63 - The three macro design steps within the Pharmaceutical Development process

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.

V.3.2 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 41 and showed an average of 36% of deliverables with an "eco-design potential", up to 43% in the research phase.

Table 41 - 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	
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%**

After this first assessment, a score between one (low environmental impact) and four (high environmental impact) was performed for each deliverable. Data in figure 64 represents the

breakdown by lifecycle stage of the level of influence of the deliverables and example of calculation is provided in appendix 7. In every step, the early development is the most 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%).

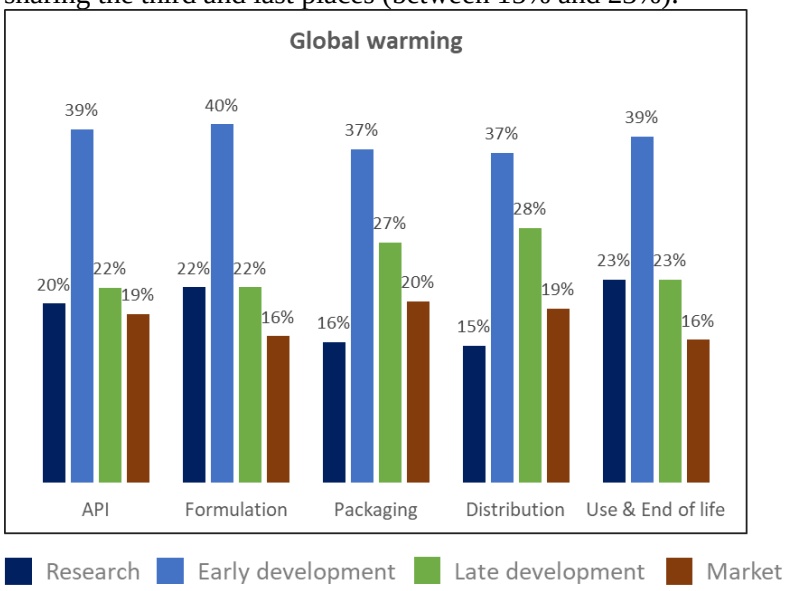


Figure 64 – Breakdown by lifecycle stage of the level of influence (%) of the deliverables of the medicine NPD, for the global warming impact per lifecycle steps (API, formulation, packaging, distribution and use & end of life), based on 263 deliverables assessed

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 8. The table 42 propose a global view with a breakdown of eco-design potential with an aggregation of the lifecycle steps.

Table 42 - 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%*	*/**	*23%*	*21%*	*3%*	*10%*	*4%*	*5%*

**Anomaly due to no clear deliverable in the list provided to the expert*

V.4 Discussion

In this part, major's highlights, convergence points and main limits are described.

V.5 Practitioners' interviews

This first study allowed 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 the 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.

V.6 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, the inclusion of those kinds of complexities was not done.

In figure 65, 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; and the eco-design potential levers of product in figure 65.

V.7 Conclusion

For R&D practitioners, a lack of understanding of eco-design approach was perceivable. Even if all interviewees are aware of the environmental issues that the Humanity is 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, major highlights and convergence points through the four main stages as it is commonly used in the pharmaceutical sector are presented.

- *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 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.

Depending on the type of the API, the ecotoxicity 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, the 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 the eco-design recommended approaches to adapt with every sub-step of the pharmaceutical NPD.

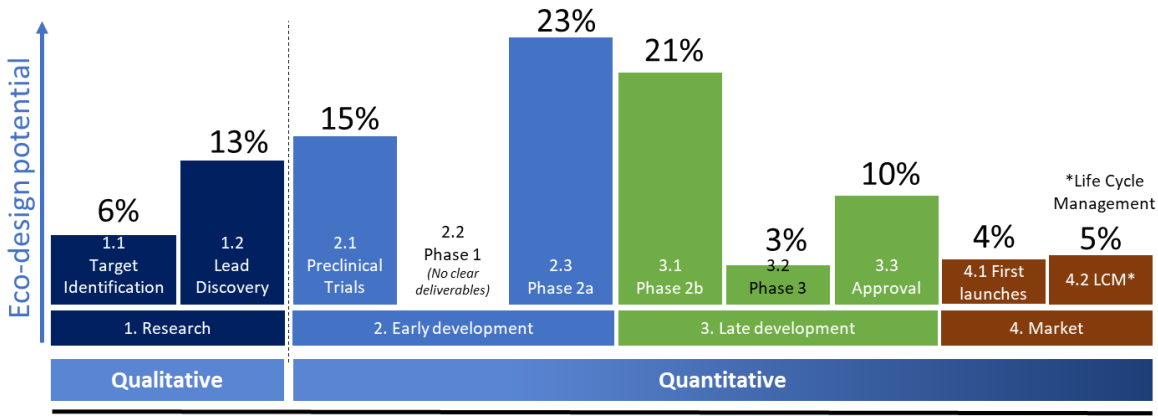


Figure 65 - Eco-design approach recommendation with the potential levers of product (average of each step of the lifecycle) per sub-step of the pharmaceutical development, for the global warming indicator

V.8 Summary of chapter 5

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.

A focus on the Meso level of the integration of eco-design as described by Brones was done. Two experimentations in order to understand where Eco-design potential levers appears in the medicine NPD process were performed. Information are 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 a first case within the pharmaceutical sector was proposed.

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.

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 possibility to engage eco-design qualitative or quantitative approaches, all along the NPD is therefore possible. 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.

In this chapter, a focus on the understanding of the pharmaceutical NPD was made, to highlight the potential levers within it. The next chapter will present research between the Meso and the Micro level, the development of a tool which aim to support and track the Eco-design practices within the pharmaceutical NPD.

Phase 3

Chapter VI

Meso approach – Eco-design maturity model

« Vous n'avez le droit d'éviter un effort qu'au nom d'un autre effort, car vous devez grandir »
Antoine de Saint-Exupéry, « Citadelle », 1948

"You only have the right to avoid an effort in the name of another effort, because you have to grow"
Antoine de Saint-Exupéry, « Citadelle », 1948

VI Eco-design maturity model, DEimeter (Drug Eco-designed integration meter)

This chapter focus on the development of an Eco-design tool who aim to support the Eco-design practices integration within the pharmaceutical sector. It contributes to the hypothesis H2.1: ***"It is possible to formalize an Eco-design maturity model for the pharmaceutical sector"***. The part VI.1 will present the context of this part. Material & methods will be presented in part VI.2. Results, Discussion and a Conclusion will be described respectively in part VI.3, VI.4, & VI.5. It is structured as shown in the figure 66.

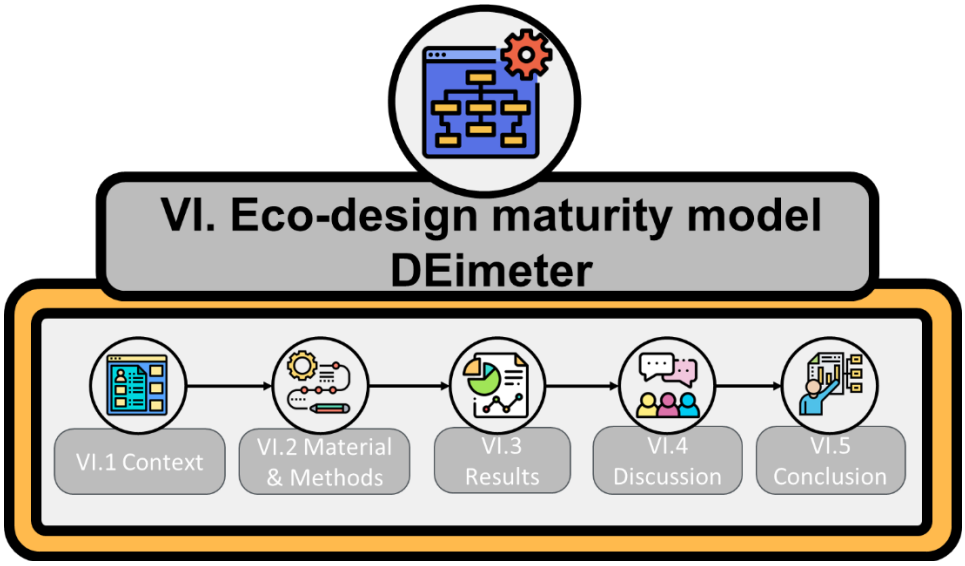


Figure 66 – Eco-design maturity model, Deimeter chapter structure

VI.1 Context

Nowadays, environmental aspects of products and services are more and more considered in their design. As described previously, the pharmaceutical sector has a singular NPD process, due to ensure the safety of patient, but do not make an exception. However, the integration of Eco-design is not fully embedded yet in this sector. The framework of Brones provides the main blocks to work on.

VI.2 Material & method

The work presented was structured with the Design Research Methodology (DRM) approach (Blessing and Chakrabarti, 2009). Each step identified in this paper can be related to the DRM framework stages and are summarized in the table 43 with related pros & cons.

Table 43 – Step of the Deimeter development correlated with the DRM framework

DRM stage (Blessing and Chakrabarti, 2009)	Step of Deimeter development	Approach and goal	Pros	Cons
Research clarification	Qualitative interview	Unstructured interview to understand overall industrial needs and define	• Let interviewee introduce topics relevant for them • More agility to explore topics	• Qualitative results • Represent point of view of interviewee

		goals (Doody and Noonan, 2013)		• Time-consuming
Descriptive study I	Literature review	Semi-systematic literature review to explore current works available in scientific community (Snyder, 2019)	• Overview of research area • Can be qualitative or quantitative • Historical overview	• Quality depends on the execution • Not exhaustive •
First prototype				
Prescriptive study	Survey	Online questionnaire to R&D managers to understand their perception regarding Eco-design & how it could be implemented (Braun et al., 2021)	• Openness and flexibility • Increase geographic scope possibilities	• Qualitative & semi-quantitative results • Lack of depth of data • Time constraints of respondents
	Eco-design expert feedback	Structured interview and questionnaire made available to explain the prototype and get feedbacks (Doody and Noonan, 2013)	• Easy process • Put interviewees at the same level • Results comparable	• Expert required • Require interviewees to deep dive the prototype • Time consuming
Second prototype				
Descriptive study II	User tests	Structured interview and questionnaire at the end of interview to explain the prototype and get feedbacks (Doody and Noonan, 2013)	• Easy process • Put interviewees at the same level • Results comparable	• Require interviewees to deep dive the prototype • Time consuming
Final version				

VI.2.1 Qualitative interview

The qualitative interview was set to feed the Research clarification. A master research student in design performed an unstructured interview (Doody and Noonan, 2013) with a senior R&D practitioner with 20 years' experience with diverse position in different phases of development. An interview in two part was made March 11th and 17th, 2022, for one hour each. Both list of topics raised, and main characteristics of the interviewee are presented in respectively Appendix 9 and Appendix 10.

The purpose of this step was mainly to understand the high-level needs of R&D managers in a qualitative manner.

VI.2.2 Literature review

The literature review was considered as the Descriptive study I of the DRM framework. It was included in the overall approach to understand the academic perspective of the Eco-design integration and maturity models topics.

A semi-systematic literature review as defined by Snyder (Snyder, 2019), was performed. The purpose was to identify main existing Eco-design tools, especially the ones regarding the integration of Eco-design. In that sense, a specific focus was done on Eco-design maturity models and generic ones. A comparison between them was done to identify the potential needs in an academic perspective and the relevance for the pharmaceutical R&D. The criteria below were defined to assess them with scores between one and three.

Table 44 – List of criteria used to assess the different maturity models

Criteria	Description	Score: 1	Score: 2	Score: 3
Precision	Refers to the scientific background of the model and the quality level of the outputs.	Broad information	Provide intermediate information	Provide deep insights
Simplicity	Refers to the structure of the model and the easiness of use	Complex, require detailed guidance	Medium, guidance might be required for several functionalities	Simple, do not require guidance
For everyone	Refers to the targeted audience of the model	For expert only	For non-expert with sensibilization	Open for neophyte
Quickness	Refers to the length of time to fill the model	Time-consuming	Require a medium amount of time	Not time-consuming
Universality	Refers to the specificities to a sector of the model	Specific to one sector	Cover several sectors	Generic

VI.2.3 R&D project managers survey

An online survey was conducted to R&D practitioners of the same multinational pharmaceutical company. The aim was to gather qualitative insights, with a significant number of respondents, of the environmental perception of R&D project managers, “if” & “how” they are currently integrating environmental aspects in their activities and “how” the integration could be fostered. The survey was conducted through Microsoft Forms between May 9th, 2022, and June 10th, 2022, the list of questions is available in Appendix 11. To make everybody at the same level of understanding, a definition of Eco-design was displayed after asking them to define it.

In 2022, the pharmaceutical company studied had 207 projects in its pipeline. If we consider that 15 managers are assigned to one project, the estimation for the targeted panel considered could be around 3 105 people. To be as relevant as possible, two formulas to calculate the size of the sample, considering the targeted panel were used. Table 45 summarizes the formulas and calculations performed.

Table 45 – Calculation of the sample size for the survey with a sampling error considered at 10%

Formula	Result	Reference
$\boldsymbol{n = \frac{z^2 \times p(1-p)}{e^2}}$	96,04	(Cochran, 1977)

$n = \frac{z^2 \times p(1-p) / e^2}{1 + (z^2 \times p(1-p) / e^2 N)}$	93,16	(Israel, 1992)

n = sample size
z = 1,96 (with a confidence level of 95 %
e = 0,1 (acceptable sampling error of 10%)
p = 0,5 (standard deviation, population of a proportion with a desired attribute)
N = population size (3 105)

As a 10% sampling error allow us to have reliable results for the interpretation, this level of acceptable sampling error was decided. The formula of Cochran does not consider the population size and lead to a more conservative result. Nevertheless, result from Israel formula is close to the previous one. In this manuscript, the conservative figure by considering an acceptable sample size with 96 answers was considered.

VI.2.4 Eco-design expert feedbacks

With the outputs of the approaches above, a first model was proposed. To be as much as relevant as possible, this model was challenged with Eco-design practitioners. This step is considered as Prescriptive study. The panel of Eco-design experts was chosen with the idea in mind to have internal experts of the pharmaceutical industry studied and external one, with no specific pharmaceutical knowledge. The table 46 summarize the main characteristics of the experts involved.

Table 46 – Main characteristics of the Eco-design panel experts

Expert n°	Affiliation	Background	Country	Scope of missions
1	Academic	• Eco-design lecturer – 1 year • Eco-design related project – 8 years • PhD in Eco-design	France	International
2	Academic	• Eco-design lecturer – 10 years • PhD in Eco-design	France	International
3	Academic	2nd year PhD student in Eco-design	France	France
4	Academic	3rd year PhD student in Management, Production, and Design	Italy	France / Italy
5	Pharmaceutical industry	6 years in pharmaceutical industry including 3 years on Eco-design related projects	France	International
6	Pharmaceutical industry	• 8 years in pharmaceutical industry, including 3 years as PhD student in Eco-design & one year as chemical technician in R&D • 3rd year PhD student in Eco-design • License degree in pharmaceutical development	France	International

The feedbacks were collected through a questionnaire that experts had to fill after an interview who were led by a master research student in design. The interviews lasted one hour and took place between May 4th, 2022 and May 23rd, 2022. Qualitative feedbacks were collected and were structured through nine key points: Utility, Consistence, Completeness, Broadness, Precision, Clarity, Objectivity, Coherence and Forecast.

With the feedbacks of the different experts, a 2nd version of DEimeter was proposed.

VI.2.5 User tests

This phase is considered as the Descriptive study II of the DRM framework. A panel of 17 R&D experts of the same pharmaceutical company was identified and seven of them engaged in the tests. They were selected due to their background and related function & knowledge regarding the medicine NPD process. Main aspects of their profiles are presented in Appendix 12.

The tests took place between June 27th, 2022, and July 5th,2022. They consisted of a one to one, with each member of the panel, for one hour. The first half hour was focused on generic presentation of what Eco-design is, the related strategy that their company was engaged for, and a presentation of the 2nd prototype of DEimeter. The second half hour was dedicated to the test and at the end, a usability questionnaire was performed to collect their feedbacks. The figure 67 summarizes the overall protocol of the tests.

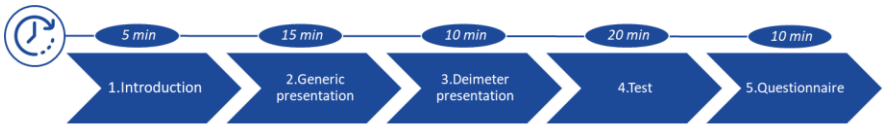


Figure 67 – Protocol steps of the tests with related durations

Participants were asked to put a score between one (strongly disagree) to seven (fully agree) through 17 statements, based on Lewis (1995), regarding DEimeter to understand how they feel to use the tool. They are listed in Appendix 13.

VI.2.6 Summary of methods

As mentioned at the beginning of this chapter, the DRM framework to structure the approach was used. Each method used within the Research clarification, the Descriptive study I, the Prescriptive study, and the Descriptive study II is presented. The aim was to ensure the quality and relevancy of outputs related to each step which is considered complementary.

VI.3 Results

In this part, the aim is to present the overall results of each step of DEimeter development, to demonstrate the relevancy of its development and to finally have a specific focus on the final version proposed.

VI.3.1 Qualitative interview

Through the semi-structured interview, qualitative results were identified and can be organized around six aspects. The results presented below reflect the point of view of the interviewee.

Overall organization of R&D

For the interviewee, there are two ways to classify R&D projects and therefore to organize the R&D. The first is to consider the steps of the development. It includes four big steps, Research, Early development, Late development, and Market. The table 47 presents the main steps and related sub-steps of the development process.

The second way is to identify the different therapeutical areas. For instance, a focus on a specific disease can be the driver to structure teams. It presents the scientific interest to address a transversal team (e.g.: physician, pharmacist, chemist, biochemist) specialized in this specific disease.

R&D process

Regardless the choice on how a company organize their teams, in term of NPD process, medicines are driven by the regulations. As mentioned above, four big steps can be identified with sub-steps. Table 47 describes the main purpose of them.

Table 47 – Main steps of the medicine NPD process

Step	Sub-step	Main purpose
Research	Target identification	Understand origin of disease and potential targets
	Lead discovery	Screen and filter molecules of interest
Early development	Preclinical trials	Test with cells, animals or informatic models
	Phase 1	Identify kinetic profile of API
	Phase 2a	Define therapeutic dose with efficacy
Late development	Phase 2b	Confirm with a larger panel
	Phase 3	Determine efficacy
	Approval	Send market authorization to local authorities
Market	First launches	Produce commercialize batches
	Lifecycle management	Ensure the availability and continuous documentation of the medicine side effects

Each pharmaceutical company follow this NPD, but they may have their own way to structure themselves to address all the regulatory requirements.

A specific point regarding the Research phase can be highlighted. Depending on the strategy of the pharmaceutical company, the Research phase can be outsourced before a purchase. This may lead to discrepancy in terms of company culture and require adaptation for the entity purchased to fit the standard of the entity purchasing.

Process iterations

The attrition rate of medicine development is high. Iterations within the NPD process exist but are limited in terms of "moving backwards". As the project development relies on many validation points before moving on the next phase, it seems key for the interviewee to identify the most important phases to assess the Eco-design maturity level to not put additional burden with no clear value, as shown in Appendix 16.

Stakeholders

The development of a medicine relies on a multidisciplinary expertise. The range of stakeholders includes project management, Chemistry Manufacturing and Controls (CMC), quality, safety, medical, value access, regulatory, clinical service operation, clinical strategy, clinical supply chain, and translational medicine. With the same philosophy of putting Eco-design effort in key phases, the CMC seems to be one of the most important roles within the R&D development processes for the interviewee.

Project governance & management

To ensure the coordination of a new medicine development, project governance is usually set. It includes control milestones and decisional points across different functions and team managers. A centralized global governance for the project and a decentralized one, more local managers, for each function coexist to ensure that every decision is based on relevant assessment at the right time. For the interviewee, Eco-design parameters could be added in the current governance process.

R&D sites

For a multinational company, it is not uncommon to have R&D sites across the world. It implies specificities such as regulations linked to the country site or even things human centric like the culture, and therefore the way of working. In the pharmaceutical sector, an additional specificity could be mentioned around "modalities". A "modality" is defined as an expertise dedicated to the development. For instance, the galenic formulation is a modality, same for the cell therapy. One site can have several modalities and focus on them.

Summary of qualitative interview result

From this interview, we can understand the importance of the medicine NPD, regulatory driven. We can see that a pharmaceutical company organize itself with the aim to set transversal teams. Both centralization of project and local point of contact coexist to ensure a flow of decision and be agile regarding local specificities as mentioned at R&D site level.

The development of an Eco-design maturity model, adapted to the pharmaceutical sector should consider therefore those aspects.

VI.3.2 Literature review

Kohlegger defines maturity models as "phases of increasing quantitative or qualitative capability changes of a maturing element in order to assess its advances with respect to defined focus areas" (Kohlegger et al., 2009). They are defined with requirements to achieve and number of levels may depends on the organization's needs (Klimkó, 2001).

As the purpose of this work was to propose a way to support the integration of Eco-design to the pharmaceutical R&D, a focus on maturity models and Eco-design ones was performed. The list below does not represent an exhaustive one regarding them. They are part of our semi-systematic review and the assessment of Eco-design maturity models identified constitute one base of the Deimeter development process. The figure 68 presents the maturity models included in this thesis with their temporalities of creation.

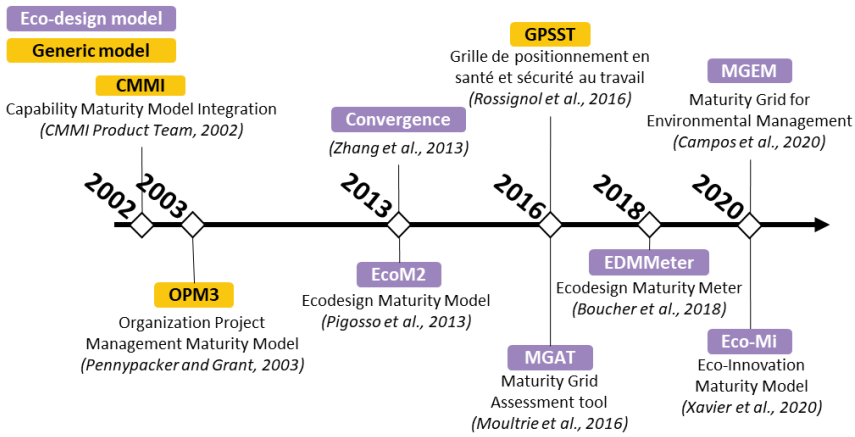


Figure 68 – Chronology of the maturity models included in this paper

Generic models

A first look on generic models was performed to understand how maturity models were generally built. As mentioned in the figure 68, "Capability Maturity Model Integration" (CMMI) (CMMI Product Team, 2002), "Organization Project Management Maturity Model" (OPM3) (Pennypacker and Grant, 2003) and "Grille de positionnement en santé et sécurité au travail" (GPSST) (Rossignol et al., 2016), which could be translated by Occupational Health and Safety Positioning Grid were studied.

Those maturity models are divided into various levels, usually from one to five, but sometimes more or less. Each level is characterized by certain requirements that have to be met (Klimkó, 2001).

The levels are also ordered sequentially from an initial (level zero or one) to an end level (level four, up to six).

In addition to these various levels, categorization is set. For instance, OPM3 propose five project management process groups: Initiating, Planning, Executing, Controlling, Closing. The GPSST is an online tool (INRS, 2022) proposed by the French National Institution of Research and Safety (INRS). They are proposing several themes to assess Training, Workplace design, Activity, Management, Communication, Assessment, and Work accident & Professional disease. The CMMI is commonly known as a framework of improvement within different applications. The CMMI for Development, the CMMI for Acquisition and the CMMI for Services can be mentioned. All of them are123rocesss model who are aiming to support respectively software development, products & services acquisition and services deployment & management (Linstedt and Olschimke, 2016).

In 2012, Wendler performed a systematic review of 237 maturity models with 20 domains (Wendler, 2012). In this part, the aim was not to have such holistic understanding. With the look of the three frameworks quickly presented, it was possible to identify a pattern with splits with relevant topics and four to six levels.

Eco-design models

In the work mentioned previously, Wendler identified at that time only three models dealing with sustainability from 1993 to 2010. In this thesis, six maturity models regarding environment, published between 2013 and 2020 was assessed. Even though we did not perform a systematic literature review as Wendler, it can be assumed that there is a growing interest regarding the environmental maturity models.

Some criteria to assess the Eco-design maturity models was set and explored. The figure 69 presents the overall results on the left and a comparison of the two top ranked models.

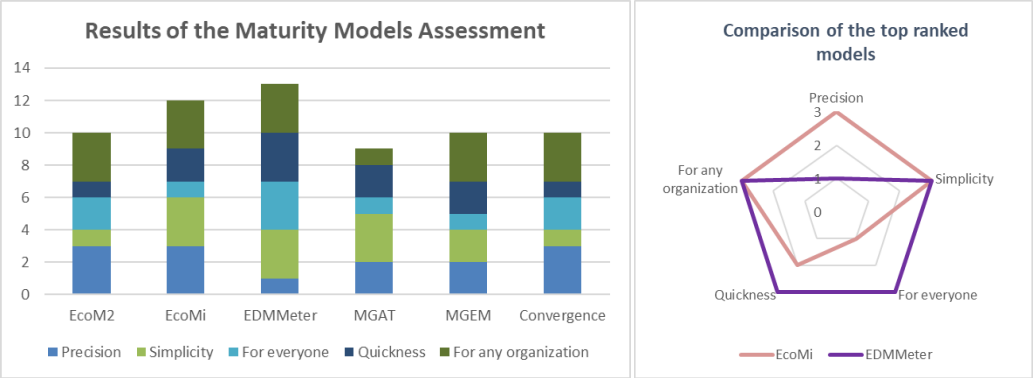


Figure 69 - Results of the Eco-design maturity models assessment & the comparison of the top two models

As an overall comment, except the MGAT model, all of them are generic ones. In other words, while MGAT is focusing on medical device products, the other models are built to not be specific to an industrial sector. We can see through the comparison of the two top ranked models that they do not share the same strengths and weaknesses. While Eco-Mi seems to be a precise model with scientific information but time consuming and cannot be filled by anyone; EDMMeter is quite the opposite by proposing a model quick to use but with results less quality than Eco-Mi.

Summary of literature review

When it comes to maturity model, the literature shows that they are supporting the evolution of a specific topic within organizations. They are usually built with levels, up to six, and with different topics considered as relevant by the users or the community.

The Eco-design field abounds of maturity models. Nevertheless, none of them are specific to the pharmaceutical industry. Additionally, our assessment is showing that there is potential room to

a proposition who could combine the strengths of Eco-Mi and EDMMeter, by proposing a model who can be filled by non-expert and who will keep relevant results.

VI.3.3 First prototype proposition

The first prototype of Deimeter was build based on the qualitative interview and the literature review. The integration model of Brones (Brones and Monteiro de Carvalho, 2015) was took into consideration by proposing to track the Meso level through the Leadership & tactical integration, the Eco-design training & resources, and finally the Collaboration & communication. The micro level is tracked with the use of Eco-design tools identified and relevant for the R&D practitioners. The figure 70 shows the overall flow and categories of Deimeter.

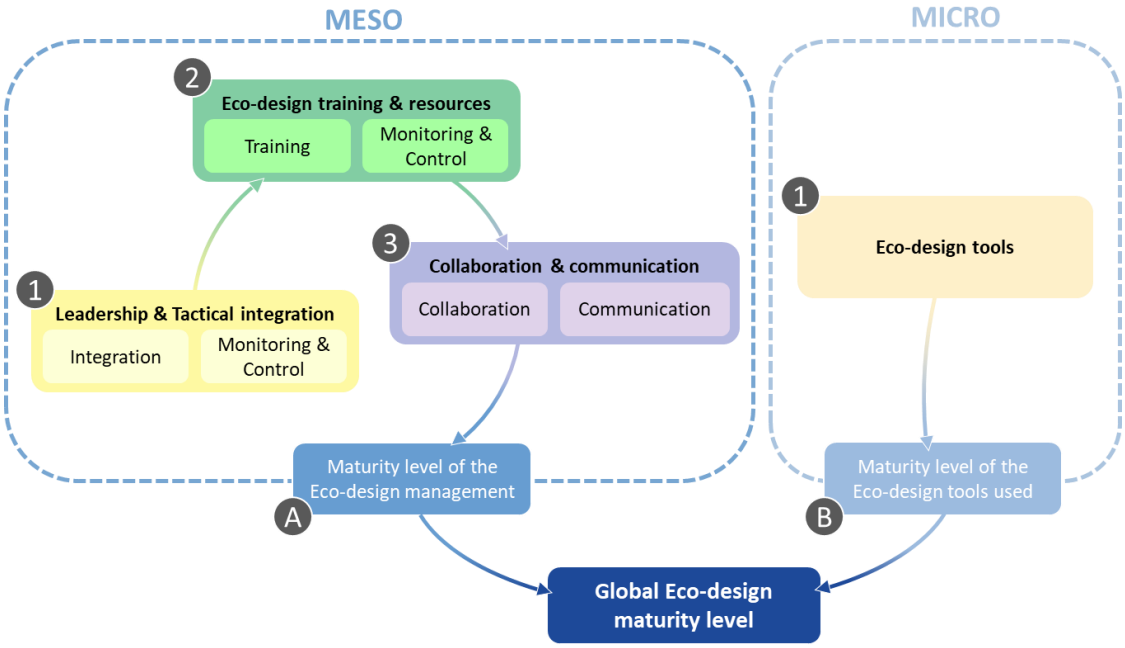


Figure 70 – Overall flow of DEimeter with the meso and micro levels of Brones

The meso part of the maturity model was established with the practices from the models of the literature review. They were identified and analyzed with the aim of outlining which ones were the most suited to the pharmaceutical NPD process. In parallel, practices were compared to avoid redundancies.

Then, the selected practices from those different maturity models were combined with the purpose of establishing a limited list of Eco-design management practices that fits into the assessment of R&D process management maturity. Finally, a total of 27 practices were identified and distributed among the categories. The list of practices is displayed in Appendix 14.

The number of practices to be evaluated by managers had to be significantly reduced to limit the time required for the use of the model. The constraint of time is a key aspect for any models in terms of use. R&D practitioners are challenged to speed up the development of product. The use of maturity models may appear as an extra burden which could lead to the non-integration of environmental aspects (Luttropp and Wadin, 2006). It can be explained by the fact that the model if for R&D practitioners with no specific knowledge in Eco-design. However, the model proposed in this thesis aims to be as precise and quick as possible, to be at the border of the scientific relevancy and industrial needs, without requiring Eco-design knowledge (Faludi et al., 2020).

The micro part is related to the use of Eco-design tools during the phases of the process. This part of the manuscript do not aim to make an exhaustive list of existing Eco-design tools as the literature abounds of it and also papers to describe them (Ahmad et al., 2018; Bovea and Pérez-Belis, 2012; Faludi et al., 2020; Lindahl and Ekermann, 2013; Pigosso et al., 2015; Poulikidou, 2012; Rossi

et al., 2020, 2016; Rousseaux et al., 2017; Schäfer and Löwer, 2021; Singh and Sarkar, 2019; Vallet et al., 2013, 2013). A way to categorize tools is to define them as quantitative, semi-quantitative, or qualitative. The correlation between the type of tools and the phases of the pharmaceutical NPD process emphasized the fact that all the tools are not always relevant for each phase. For instance, quantitative tools (e.g., LCA) cannot be used during the early stage of the process due to the lack of available data. One of the biggest aspects of our model aim to help project stakeholders in the identification of the most suited Eco-design tools regarding their function and the concerned project phase.

VI.3.4 Survey

The survey took place in the same pharmaceutical company, with 129 participants. It exceeds the sample size targeted of 96 answers and results can be considered as exploitable. In this paper, a focus was done on key outputs of the survey. Information regarding characteristics of respondents is presented in Appendix 15. 92% of the respondents claims to be familiar with the overall R&D process. In terms of Eco-design understanding, the figure 69 shows that 29% of participants gave a wrong definition and 18% declared to have no idea. To be considered as "perfect", respondents must have written in their answer notions of "lifecycle perspective", "holistic environmental impact" and "reduction of the environmental impact", with same or similar wording. The classification "aware" is considered when they do not have included all those aspects.

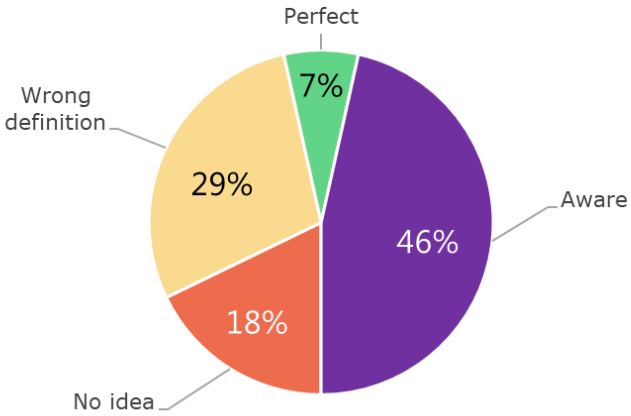


Figure 71 – Repartition of understanding of the Eco-design concept among R&D managers

Despite the lack of Eco-design understanding of 47% of participants, 99,2% of them consider this approach important and 98,5% as the future of designing products. Despite this common view, apprehension is perceivable where 41,9% of respondents answered that Eco-design will complicate the process as shown in figure 72. Additional verbatims regarding their perceptions of which choices during the project phases have impacts on the environmental profile of the final product are presented in Appendix 16.

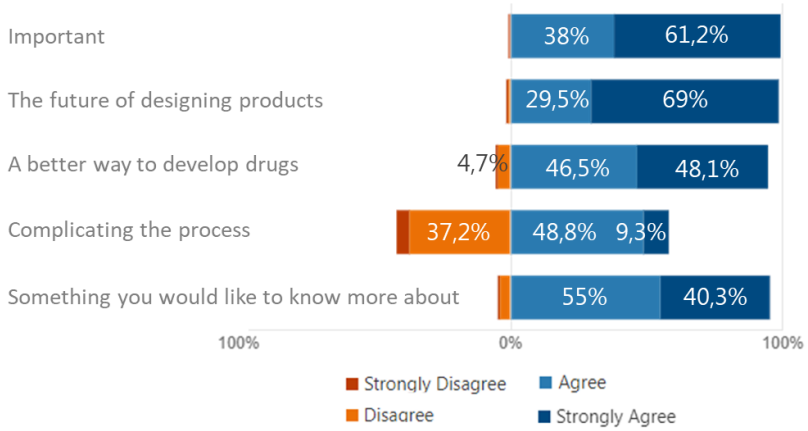


Figure 72 – Eco-design perception of R&D managers

To the question of the implementation of Eco-design, 74% of respondents consider that it is not part of the current way of working. The figure 73 is showing the constraints that R&D managers are facing. The "other" pilar include "not enough information", "lack of awareness" and "budget / cost". Verbatim is proposed in Appendix 17 to the "other" option.

Figure 73 – List of constraints that R&D managers are facing to implement Eco-design

We can understand that the information is key for R&D managers. To the integration within governance committees, 33% of respondents consider that it should be in Development Strategy Governance, as illustrated by the figure 74.

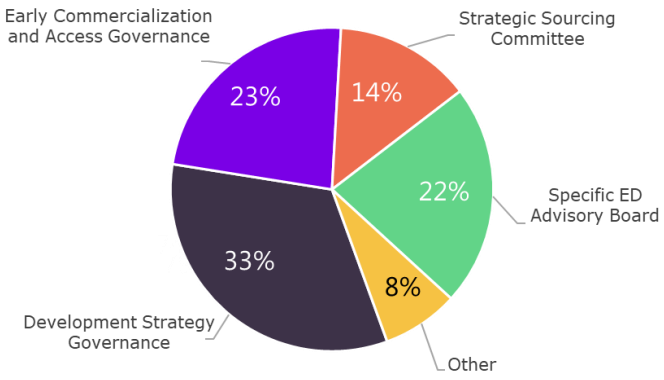


Figure 74 – Committees where Eco-design information could be integrated

Summary of the survey

Despite a lack of knowledge of Eco-design, R&D managers seem to be willing to integrate this approach in their way of working. A level of apprehension is perceivable through this survey, especially with extra workload expected from some of the respondents. A support is clearly identified as needed, with trainings, tools, communication, and additional resources.

VI.3.5 Eco-design expert feedbacks

As mentioned in part 3.4, experts were asked to assess the prototype through nine aspects between “unsatisfactory”, “needs improvement”, “satisfactory”, “very satisfactory”. The results are displayed in the figure 75, by considering “unsatisfactory” & “needs improvement” as negative and “satisfactory” & “very satisfactory” as positive in the breakdown.

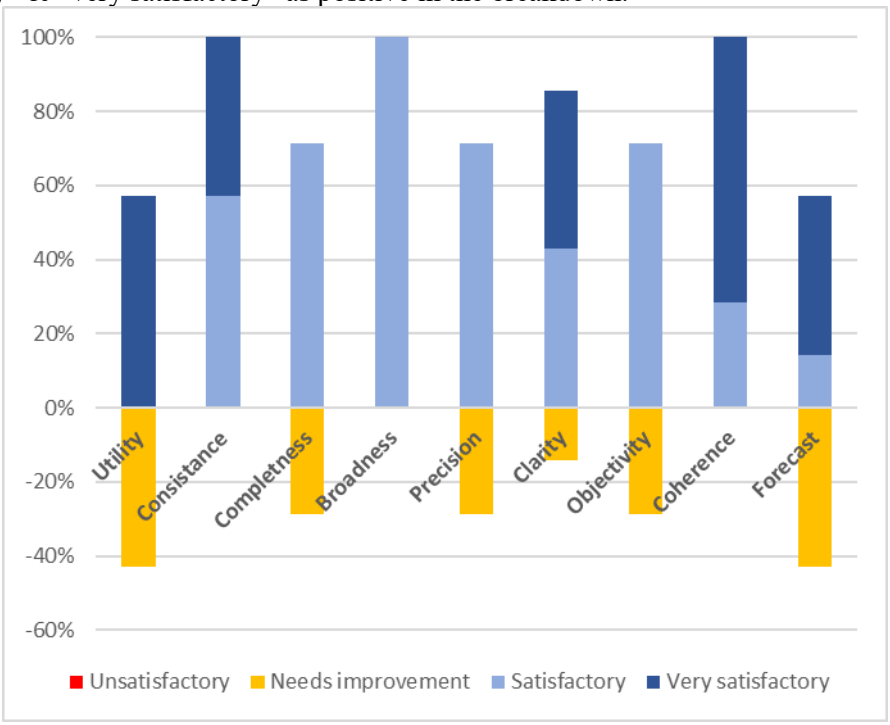


Figure 75 – Breakdown of the expert feedbacks regarding the first prototype of DEimeter

We can observe that, for the consistence, the broadness and the coherence, the propositions do not present issues. The completeness, the precision, the clarity, and the objectivity seem to be improvable. Even if none of the experts considered “unsatisfactory” the propositions, a specific focus could be identified for the utility and the forecast parameters of the tool.

In addition of the assessment presented in 4.5, qualitative feedbacks were also provided. A shared comment is around the potential addition workload to fill the tool, which will not be spend on action plans.

VI.3.6 Second prototype proposition

Based on the feedbacks of the experts, a second proposition was made to satisfy the issues regarding utility and forecast. As such, an additional matrix in five levels was proposed, to define the organizational and operational dimensions. The Appendix 18 is summarizing the main aspects of the levels.

VI.3.7 User tests

A first part of the tests aimed to assess the usability of DEimeter. A second aspect was explored around the organizational dimension, to see how the users managed the practices proposed. It is indeed key in design to include future users to design systems who fulfil their needs (Gulliksen et al., 2003).

The overall feedbacks show that the tool answer the expectations of R&D managers. With the sum of all notations of the 17 statements by the seven participants, an 81% level of satisfaction can be identified. The overall scorings and calculations are available in Appendix 19. For users all practices are currently not relevant for each function of the medicine NPD.

VI.3.8 Summary of results

To develop DEimeter, the maturity model for the pharmaceutical sector, complementary approaches were performed, structured through the DRM framework. Despite the singularities of the pharmaceutical development, their practitioners and managers are facing similar blocking points that are described in the literature regarding Eco-design implementation. It is also key for them to adopt this approach for the future of pharmaceutical R&D. The development of DEimeter considered their insights but also the ones of Eco-design experts.

VI.4 Discussion

In this part, the aim was to take a step back regarding results exposed previously and propose discussions regarding some aspects. Major's highlights and limitations of the overall approach will then be described.

VI.4.1 Qualitative interview

The unstructured interview performed highlighted the complexity of the medicine NPD process. The overall framework is well known, especially due to the regulation. The way of how companies are managing it is however discreet, probably due to keep competitivity against peers. Despite that assumption, it can be assumed that the description made by the interviewee can fit the organization of several pharmaceutical companies. Indeed, even if each company has its own culture, the porosity in terms of human resources, due to the high turnover (Sharma et al., 2021), may lead to a harmonization in terms of overall way of working. The diversity of stakeholders is also contributing to this complexity. Transversal teams are working to develop drugs, with knowledge discrepancies and especially in terms of environmental aspects.

The main limitation of this part is linked to the approach itself. As any unstructured interview, qualitative results are available. And as they represent the interviewee point of view, they should be taken carefully.

VI.4.2 Survey

The sample size of 129 respondents exceeds the threshold value of 96 to have a 10% margin of error. Therefore, results can be considered as exploitable. Almost all R&D managers are currently convinced of the necessity to include the environmental parameters into their design process. It shows a clear change of paradigm, where previously the environmental aspects were not an element strongly integrated. For instance, in 2006, the European Medicines Agency stated in one of its guidelines regarding ERA, that "in any event this impact should not constitute a criterion for refusal of a marketing authorization" (EMEA, 2006). The change of paradigm is also perceivable at the European level, like through the proposed taxonomy where environmental aspects are defined for medicine products (Platform on Sustainable Finance, 2021b).

Even if approaches to include environmental aspects into medicine products, such as Green chemistry or ERA, exist since years, majority of respondents considered that Eco-design approach are not embedded yet. It can be explained by the fact that those approaches do not usually consider neither a lifecycle perspective nor the holistic environmental aspects.

It is also interesting to see that usual constraints regarding Eco-design implementation are identified, such as trainings, resources, or the apprehension regarding the additional workload and complexity (Rossi et al., 2016).

VI.4.3 Eco-design expert feedbacks

The feedbacks gathered were based on a first prototype. Therefore, some aspects of the tool were incomplete in terms of development, such as the interface. It could have been a bias, especially regarding the workload / easiness of DEimeter.

Two participants provided qualitative feedbacks but did not fully fill the questionnaire. The nine aspects in 4.5 is therefore incomplete in the sense of they did not want to position themselves without of a use case for DEimeter.

VI.4.4 User tests

In this part, a focus on how users managed the tool, with both the navigation and the content inside it was done. The lower scorings (four on a scale up to seven), are related to the information. Especially the ones displayed, the readability and easiness to find them. It can be explained by the novelty of DEimeter which, like any new tool, require a time of adaptation. Nevertheless, based on the scorings of the different users, it can be assumed that the current proposition of the functionalities and how DEimeter display results could fit most of the needs of R&D practitioners and managers. As mentioned in the results, participants claimed that practices are not relevant to each function. In other words, a work to adapt practices to function is required. It can be explained by the fact that each function does not have, both the same goals and ways of working.

VI.4.5 DEimeter final version

The final version of DEimeter proposes to track the integration of the organizational dimension of Eco-design through 22 practices, split into three categories: Leadership & tactical integration, Eco-design training & resources, and Collaboration & communication.

The second aspect is regarding the operational dimension, which is tracked with the use of relevant tools in accordance with each step of the development process. Within DEimeter, it is possible to navigate inside each step of the medicine NPD (e.g., research, preclinical trials, phase 1) to then select a function (e.g., CMC, regulatory). A mapping of relevant families of Eco-design tools is displayed, specific to the step and think regarding key functions. The figure 76 presents the dynamic workflow of DEimeter operational dimension.

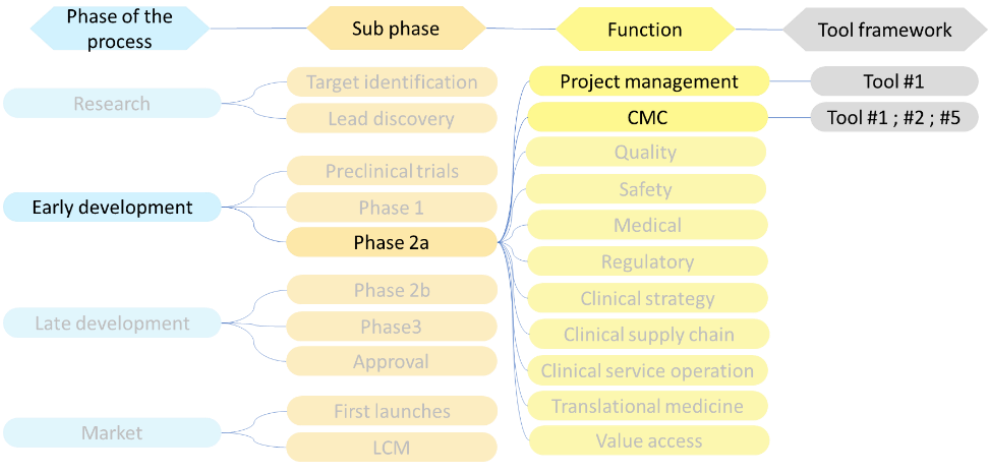


Figure 76 – Example of dynamic workflow of DEimeter operational dimension from Early development, including phase 2a to tools framework for Project management and CMC

It is therefore possible through these two dimensions to set a level of integration, from an organizational perspective, but also operational one. Even if the potential of Eco-design of each stakeholder was identified, in terms of phases, the main potential is between phase 2a and 2b. Therefore, a specific focus was performed during these phases and to functions identified as key by the interviewee during the unstructured interview.

VI.5 Conclusion

In parallel of making medicine available, the pharmaceutical has the societal duty to prevent the environmental burden of its activities. Nowadays, pollution of rivers with drugs or related products is at alarming levels. Additionally, the pollution of the pharmaceutical need to be consider from a lifecycle perspective and with a holistic perspective in terms of environmental impacts. Even if the integration of environment is not new in this industry, the Eco-design perspective is not a well embraced in mindsets.

The Design Research Methodology framework structured the development of a tool, which feed the hypothesis "Eco-design maturity model can be adapted for the pharmaceutical development".

Through an unstructured interview, a semi-systematic literature review, a survey to R&D project managers, with Eco-design expert feedbacks and some user tests, the Drug Eco-designed integration meter tool was proposed. The DEimeter tool is an Eco-design maturity model, split in two dimensions, organizational & operational, with five levels each. The two dimensions are addressing the Meso level and the Micro one of the frameworks of Brones. The levels are set to support the evolution of practices. For the organizational dimension, 27 practices are identified. The operational dimension is defined adequately to each step of the medicine NPD and stakeholders. By using practices and tools identified in DEimeter, managers can track the level of integration of Eco-design within each step of development.

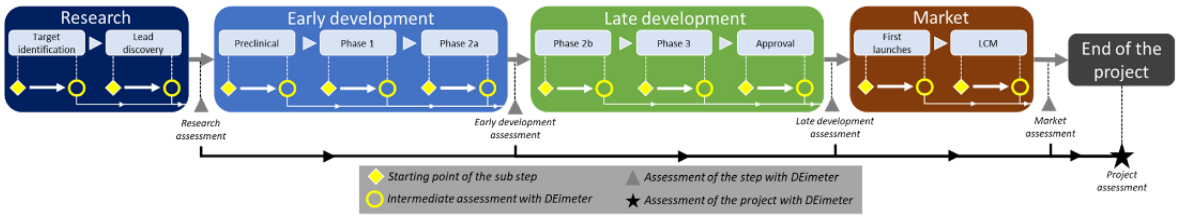


Figure 77 – Medicine NPD process with the proposed use of DEimeter

VI.6 Summary of chapter 6

The integration of Eco-design into companies' practices is a key challenge to Eco-designed products.

In this chapter, the Meso level of the integration of eco-design as described by Brones was in focus. An Eco-design maturity model was developed, adapted for the pharmaceutical industry so their practitioners can take ownership of the Eco-design approach, the Drug Eco-designed integration meter (DEimeter).

The development of the tool was structured with the DRM methodology. Qualitative interview, to set an overall understanding of the R&D process, a literature review, a survey to R&D practitioners, feedback from Eco-design experts regarding the beta version of the tool, and users tests were performed.

Results from the survey showed that R&D practitioners are not familiar with the concepts of Eco-design, but they estimate this approach as necessary and are willing to integrate it more in their practices. They highlighted a lack of trainings and tools regarding Eco-design. Some fear regarding the additional workload was also mentioned during the survey.

The tool developed aim to track and support the integration of Eco-designed into practices. In other words, the focus of the mean obligation, as the performance obligations can be assessed with analytical tools who are quantitative (e.g.: LCAs). DEimeter is structured in two dimensions, the

organizational and the operational one. The first dimension aims to support the managerial practices while the second one is providing tools depending on the step of the R&D process.

The first version of DEimeter can be improved by adapting it more to either specific stakeholder of the R&D process (e.g.: galenic formulation team, chemist, analytics) or to specific medicine families (e.g.: monoclonal antibody, chemical, mRNA).

After this proposition of an Eco-design tool to support its practices within the pharmaceutical NPD, the next chapter will focus on another side of the Micro dimension, guidance to assess the environmental impacts of medicine products.

Phase 3

Chapter VII

Micro approach – Monoclonal Antibody Product Category rules proposition for LCA

« Si vous ne pouvez pas le mesurer, vous ne pouvez pas l'améliorer »
William THOMSON, Lord KELVIN

"If you can't measure it, you can't improve it"
William THOMSON, Lord KELVIN

VII Monoclonal Antibody LCA guidance

In this chapter, the Micro part explored during the PhD will be exposed, the proposition of main aspects to take into account when performing an LCA, with a focus on monoclonal antibodies (mAbs), through a Life Cycle Assessment (LCA) performed. This chapter propose a description of technical aspects of Mabs products before to deep dive in the experimentation. A presentation of the mAbs is suggested in part VII.1 to then focus on the LCAs performed for such products in part VII.2. Results, Discussion, and Conclusion of our research are then presented respectively in part VII.3, VII.4, and VII.5. The figure below presents the overall flow of this chapter.

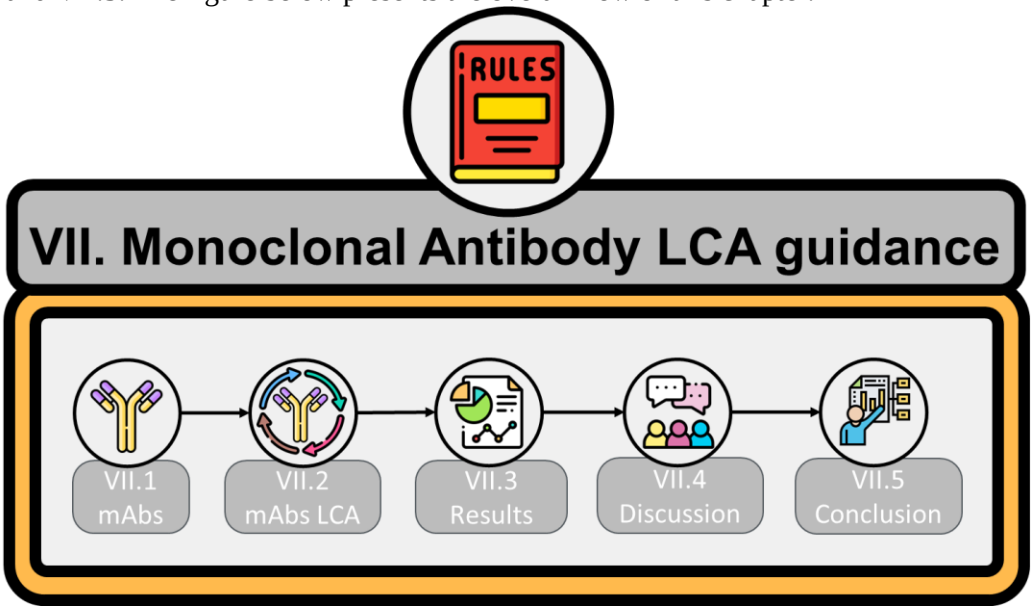


Figure 78 – Monoclonal antibody LCA guidance chapter structure

VII.1 Monoclonal antibodies

VII.1.1 Definition

First monoclonal Antibody (mAb) was discovered in 1975 by Kohler and Milstein (Nissim and Chernajovsky, 2008) and the first one licensed in 1986 (Liu, 2014), Orthoclone OKT3 (muromonab-CD3). Several definitions can be found for the mAbs:

United States

- National Institute of Health, National cancer institute

"A type of protein that is made in the laboratory and can bind to certain targets in the body, such as antigens on the surface of cancer cells. There are many kinds of monoclonal antibodies, and each monoclonal antibody is made so that it binds to only one antigen. Monoclonal antibodies are being used in the diagnosis and treatment of many diseases, including some types of cancer. They can be used alone or to carry drugs, toxins, or radioactive substances directly to cancer cells."

- FDA

"Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful antigens such as viruses" (Commissioner, 2020)

"Monoclonal antibodies are immunoglobulin molecules secreted from a population of identical cells (i.e., cloned cells)" (FDA, 2011)

Europe

- EMA

"Monoclonal antibodies are immunoglobulins (Ig) with a defined specificity derived from a monoclonal cell line. Their biological activities are characterized by a specific binding characteristic to a ligand (commonly known as antigen) and may be dependent on immune effector function such as antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Monoclonal antibodies may be generated by recombinant DNA (rDNA) technology, hybridoma technology, B lymphocyte immortalization or other technologies (e.g., display technology, genetically engineered animals)." (EMA, 2016)

Literature

"Special molecules in our blood and tissue fluids that help us fight infection. There are a variety of antibody molecules of different shapes and sizes, although the basic structure is essentially "Y" shaped, with the two tips designed to recognize and bind foreign agents (for example, bacteria), foreign substances, or harmful cells." (Nelson et al., 2000)

"Monoclonal antibodies are therapeutic protein molecules used to bind specific antigens in the body." (Kannan et al., 2019)

"Laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on cancer cells" (Bayer, 2019)

For the rest of the manuscript, mAb will be define as:

"Monoclonal antibodies are therapeutic protein molecules, laboratory made, engineered to serve as substitute antibodies that can restore, enhance, or mimic the immune system's"

Such products can be classified in four categories: murine, chimeric, humanized, and human (Bayer, 2019). The table 48 present the description of those categories.

Table 48 - mAbs categories, based on Bayer (Bayer, 2019)

Category	Description
Murine	• *Uses harvested B lymphocytes from mice that are fused with an immortal myeloma cell line lacking the hypoxanthine-guanine-phosphoribosyl transferase gene.* • *Allergic reactions are common in humans, with potential limited benefit because of a short half-life* • *Ends in -omab*
Chimeric	• *Approximately 65% human derived, 35% murine derived, uses murine antigen-specific variable region, and heavy and light chains of human.* • *Demonstrate extended half-life in human with reduced immunogenicity; still able to induce antidrug antibodies* • *Ends in -ximab*
Humanized	• *Murine hypervariable regions of the light and heavy chains are fused onto a human antibody framework; approximately 95% human.* • *Has decreased production of anti-drug antibodies; limitations because the process to create is difficult* • *Ends in -zumab*

Human	• *Fully human monoclonal antibodies.* • *Less antigenic and better tolerated; appear to have the longest half-life in humans* • *Ends in -umab*

More basically, mAbs can be used to treat various diseases (e.g.: breast cancer, leukemia, asthma, macular generation, arthritis, Crohn's disease), but also for diagnosis purpose (e.g.: pregnancy, menopause, heart attack), and even to help routine hospitals practices (e.g.: blood transfusion, organ transplantation) (Quinteros et al., 2017).

VII.1.2 Authorized by the FDA and EMA

In this part, an overview of the mAbs authorized in the US and in Europe is proposed. Two databases mentioned in the table 49 was explored, with related documentations available.

Table 49 - database used to gather information related to authorized mAbs

Region	Entity responsible	Documents used	Link
US	FDA	Label	https://www.accessdata.fda.gov/scripts/cder/daf/
Europe	EMA	EPAR – Product information EPAR – All authorized presentations	https://www.ema.europa.eu/en/medicines

In 2021, the FDA had in its database 126 mAbs authorized. For Europe, the EMA had 111 ones. Some of the mAbs included were only marketed in Europe or US, and some of them were both. 153 different brands of mAbs for both US and Europe can be identified. The current authorized mAbs were made available in the markets between 1994 and 2021 has shown in the figure below.

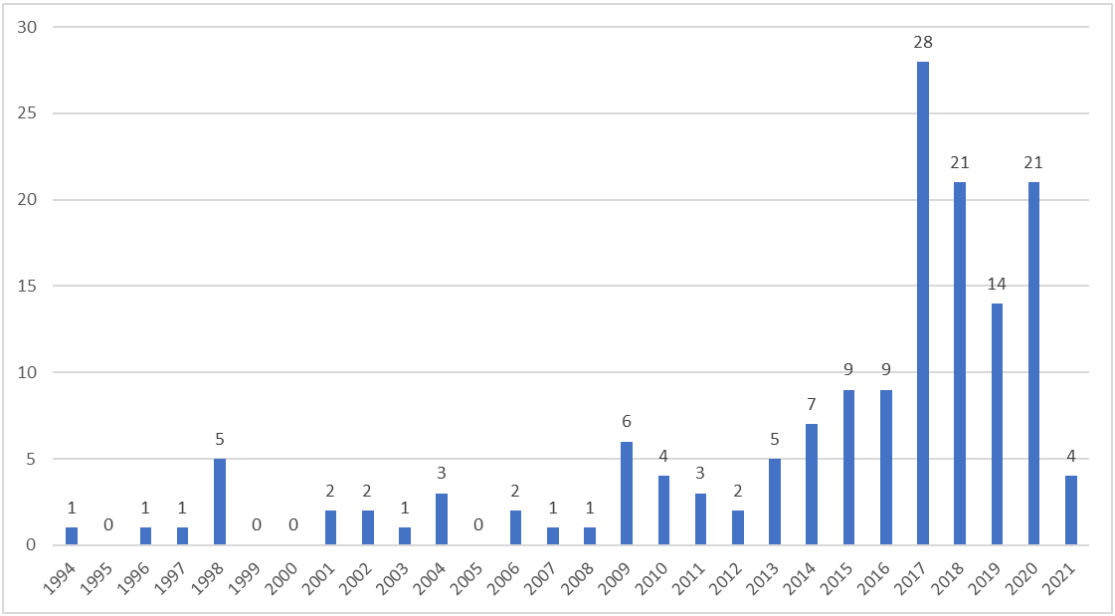


Figure 79 - Repartition of the number of mAbs assessed regarding the year of their authorization

It is possible to identify the companies who are holding the mAbs in quartiles. With 11 mAbs in its portfolio, Roche seems to be the leader in this field, followed by Amgen, Jannsen, Novartis and Pfizer. They are constituting a first quartile. The other ones are listed in the table below.

Table 50 - Quartiles of companies holding authorized mAbs in Europe & US

Quartile	Number of mAbs in the portfolio	Companies
Q1	9 to 11	Roche, Amgen, Janssen, Novartis, Pfizer
Q2	5 to 8	Genentech, Samsung Bioepis, Sanofi, Celltrion Healthcare, Astrazeneca, Eli Lily, GSK, Sandoz
Q3	2 to 4	Bristol-Myers Squibb, Merck Sharp and Dohme, Regeneron, Takeda, Teva B.V., Abbvie, Alexion, Biogen, Boehringer-Ingelheim, EUSA Pharma, Kyowa Kirin, Merck KGaA, UCB Pharma
Q4	1	Accord Healthcare S.L.U, Astellas, Ceft Biopharma, Curium, Cytogen, Daiichi Sankyo, Elusys Therapeutics, Fresenius Kabi Deutschland GmbH, Gilead Sciences, Horizon Therapeutics, Leo Pharma, Lundbeck Seattle Biopharmaceuticals, MacroGenics, MorphoSys, Novimmune, Ridgeback Biotherapeutics, SFL Pharma, Stada Arzneimittel AG, Theratechnologies, United Therapeutics, Valeant Pharmaceuticals Luxembourg, Viatris, Viatris , Viela Bio, Y-mAbs Therapeutics, Zoetis

In 2015, mAbs market value was estimated at US$115,2 billion and forecast for 2025 is predicting and growth at $300 billion as described by Lu (Lu et al., 2020).

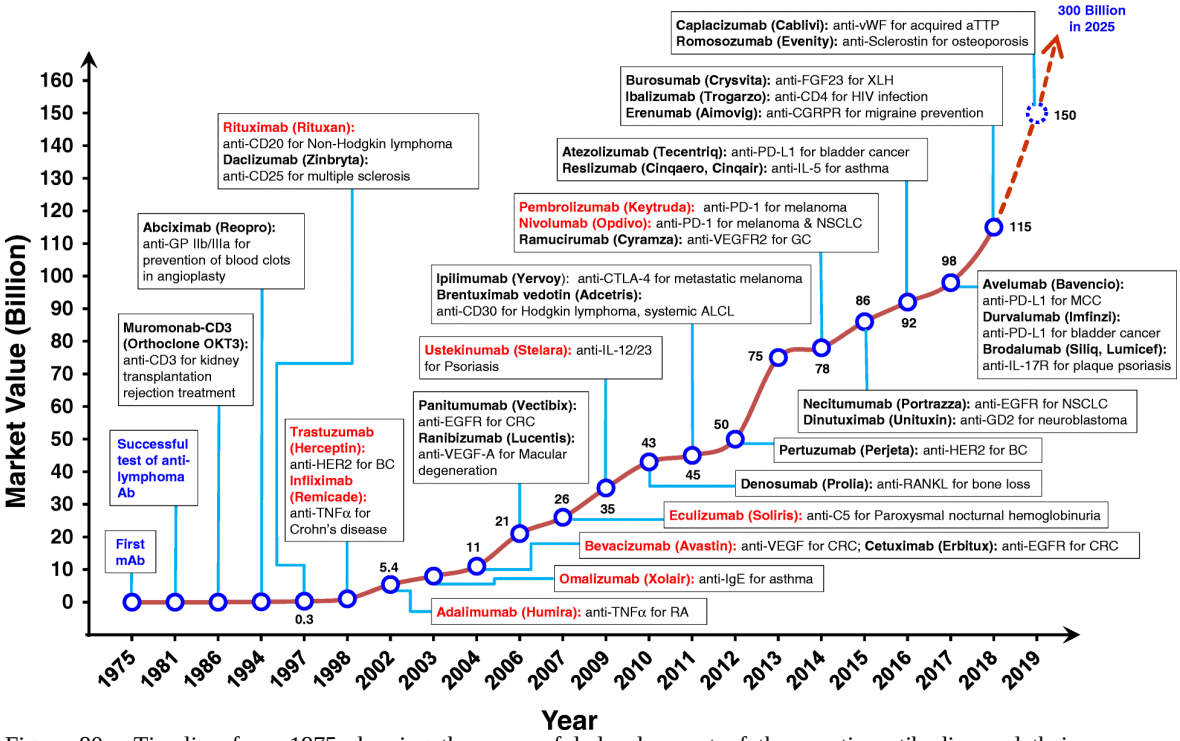


Figure 80 - Timeline from 1975 showing the successful development of therapeutic antibodies and their applications from Lu (Lu et al., 2020).

VII.2 Monoclonal antibodies LCA

In this part, the work performed around the LCA of mAbs will be presented. A literature review is proposed, and a second part focus on the life cycle steps of a mAbs. Then, a third part present the LCA performed to then conclude about the overall aspects.

VII.2.1 Literature review

In this chapter, the review regarding generic guidance to perform LCA or similar for medicine products and the LCA of mAbs available in the literature is presented.

Generic guidance to perform LCA or similar for medicine

The Product Category Rules (PCR) are key documentation who guide the analyst to perform LCAs and enable the external communication possibilities through the Environmental Product Declaration (EPD). Several platforms who are making available existing PCR were explored and currently, only one official PCR can be found. This product category rule cover *"Blood and blood derived products for therapeutic or prohylactic uses"*, as shown with the System boundaries form this PCR in figure 81. It was developed in 2016 by INDACO2, a consulting firm who support companies in the environmental assessment and communication. The PCR was updated the 14th march of 2022 (INDACO2 SRL, 2022).

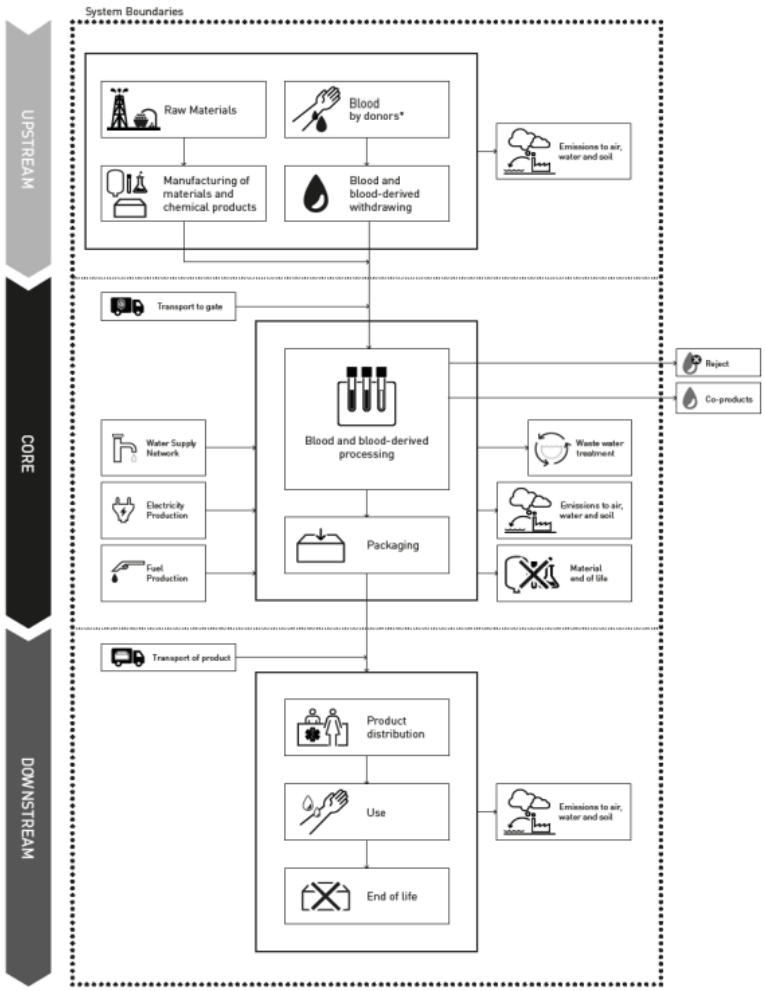


Figure 81 - System boundaries from the PCR of INDACO2 (INDACO2 SRL, 2022)

Earlier, in 2012, the consulting company ERM had developed for the NHS a guide to perform GHG emission assessment (Allison et al., 2012). They involved pharmaceutical companies such as AstraZeneca, Baxter, GSK, Johnson&Johnson, Novo Nordisk, and Pfizer. In this guideline, they have considered different type of API, the synthetic organic chemicals, the cell culture, the egg-based cultivation, the conjugates vaccines, the plant-based extraction, and the animal & human derived based medicines. In parallel, they have set guidance for several galenic forms such as the solid dose, the liquid dose, the creams and ointments, the patches, the gases, and the administering devices. This guideline proposes qualitative guidance to perform a GHG emission assessment. It is structured around an example of process map for each type of API, such as in the figure 82, elements to include in the process and the one to exclude.

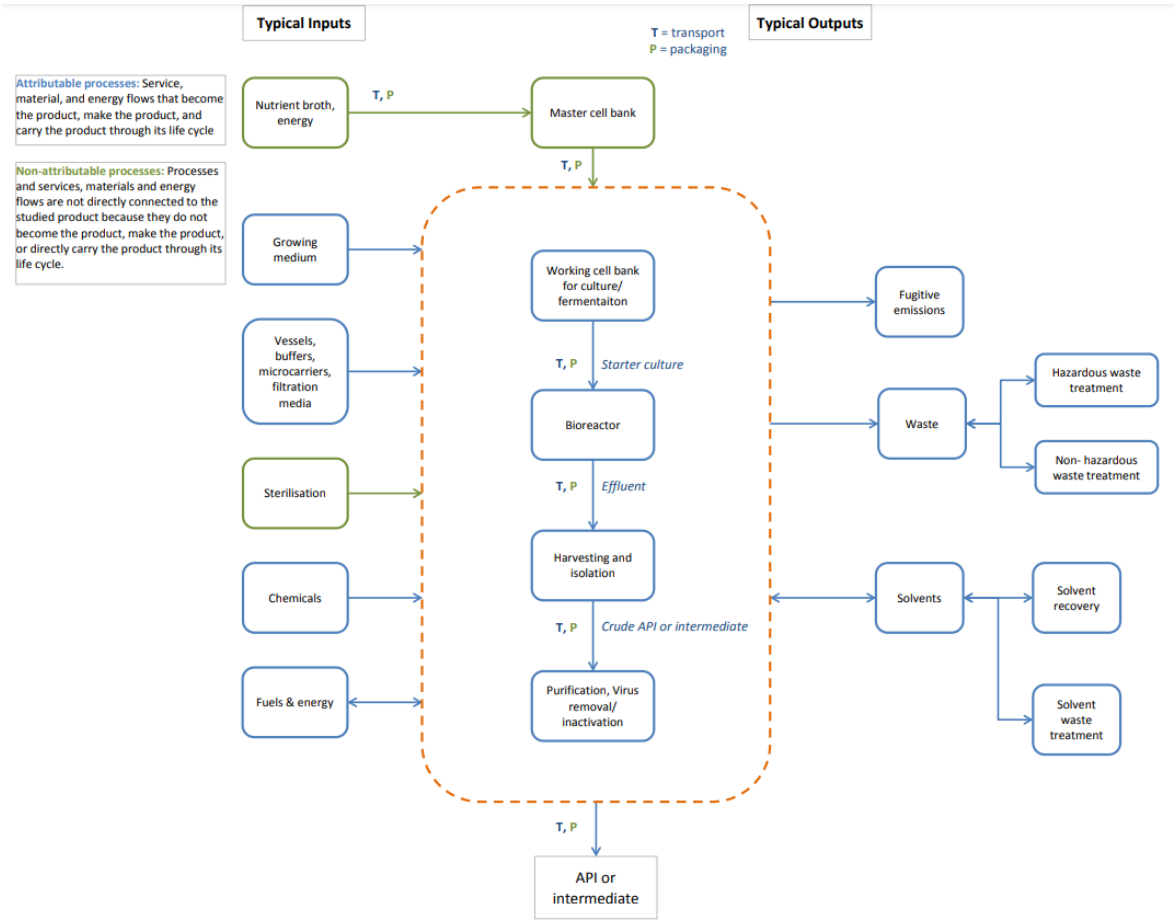


Figure 82 - example of process map for cell culture API (Allison et al., 2012)

Not available anymore, a PCR on *"Vaccines for human or veterinary medicine, whether or not put up as medicaments"* was developed in 2013, for the purpose of a pig vaccine LCA (Moraes et al., 2013) communication through an Environmental Product Declaration (EPD) (Pfizer, 2012).

Finally, the TU Berlin worked on a development of a PCR for pharmaceutical product and processes (Siegert et al., 2019). Even if they did not publish this document in official PCR platforms, they made their document available. Unlike the other documentation described above, the authors are providing ways to fill some data gaps (e.g.: formulas or default data). However, two main limitations can be highlighted, the German centric solutions to fill data gaps and the chemical-API focus. Despite those limits, the PCR remain a first relevant base to be able to perform LCA.

mAbs LCA in the literature

As described in the state of the art (chapter II.5.3), the scientific literature does not abound of pharmaceutical LCAs. Four papers are describing LCAs for monoclonal antibodies and one other for injectable vial glass (Belboom et al., 2011), which is usually used for mAbs. Even if the Functional units were different, it is possible to identify five values of kg CO2-eq / kg of API within three studies. The study of Pietrzykowski et al. focused on a comparative assessment and they did not display any quantitative results (Pietrzykowski et al., 2013).

Table 51 - Comparison of LCA results of available papers, for the climate change indicator (IPCC GWP 100a)

	kg CO2-eq / kg of API	Reference
mAb A	31000	(Renteria Gamiz et al., 2019a)
mAb B	20000	(Renteria Gamiz et al., 2019a)
mAb D	22700	(Budzinski et al., 2022)
mAb E	276600	(Amasawa et al., 2021)

mAb F	137230	(Amasawa et al., 2021)

Even if the values are high, the range of differences (between a factor 12 and 14) seems to be lower than compared to what can be found for chemical products (see chapter II.5.3, table 26). It can be explained by the fact that the process to produce mAb is similar to a mAb from another.

VII.2.2 Life cycle of a monoclonal antibody

In this part, the terminology "life cycle" is considered as it is defined in the LCA community and not the one in the LCM one. The ISO 14001 defines a "life cycle" as below (ISO, 2015):

"Consecutive and interlinked stages of a product (or service) system, from raw material acquisition or generation from natural resources to final disposal. Life cycle stages include acquisition of raw materials, design, production, transportation/delivery, use, end-of-life treatment, and final disposal."

To understand the different life cycle steps of the mAbs, an understanding of the different format possible available in the market is required. In the previous chapter, 153 brands of mAbs were identified. For those brands, 239 marketed forms available were identified. For instance, one same brand can be sold in a pre-filled syringe, a pen, or a vial. Finally, the pre-filled syringe can be packed in a carton containing two devices and another one three. This additional layer leads to 548 marketed products. The figure below lists the different pharmaceutical forms available for the mAbs. More than 86% of the products are in liquid form, either for injection (71%) or infusion (16%) within the 548 marketed products is perceivable.

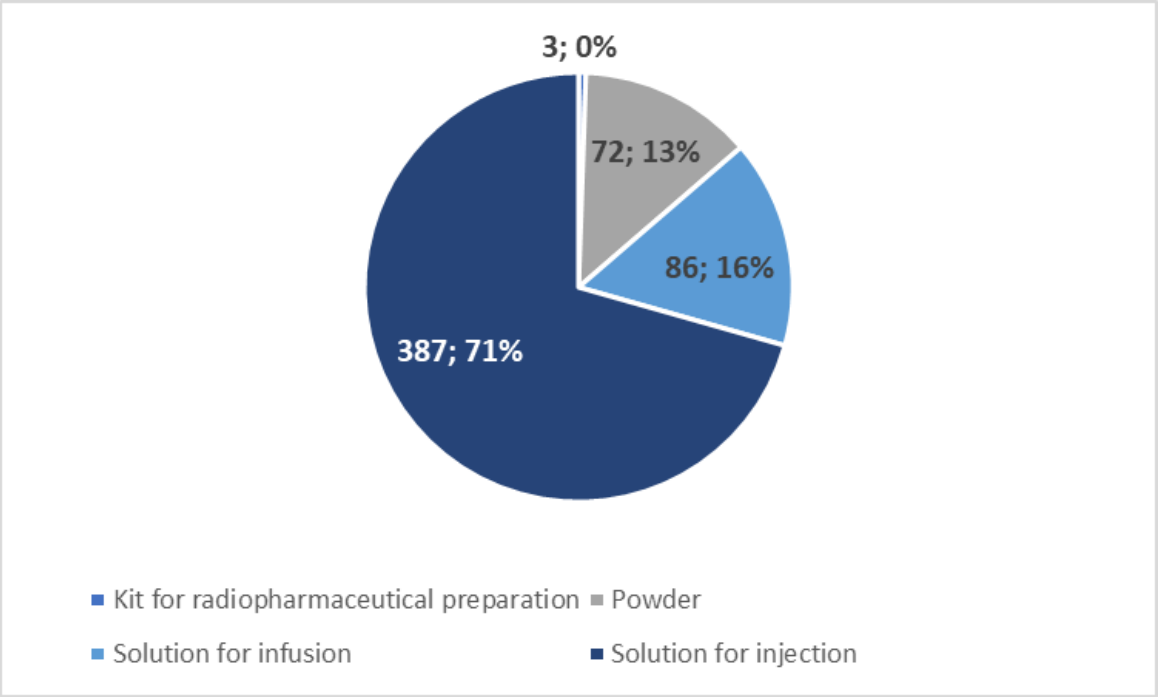


Figure 83 - Repartition of the pharmaceutical forms of the 548 marketed products available

Regarding the primary packaging, four types were identified within the 548 marketed products available: the vial (44%), pre-filled syringe (33%), pre-filled pen (22%), and cartridge (0,4%).

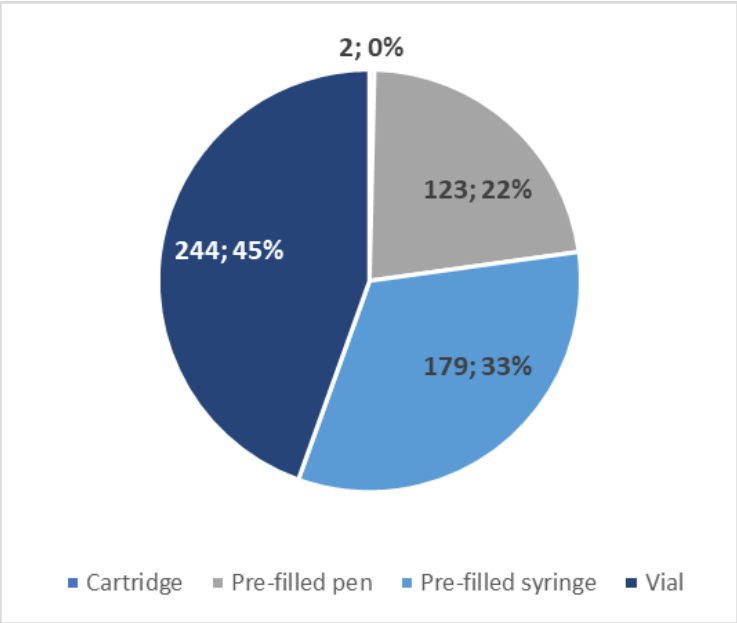


Figure 84 - Repartition of primary packaging of the 548 marketed products available

These different pharmaceutical forms and packaging may lead to different inputs and outputs at each step of the life cycle. An overview on them is proposed below.

Raw material

In this part of the chapter, some considerations regarding the raw materials required to produce mAbs are suggested, as illustrated in the figure 85.

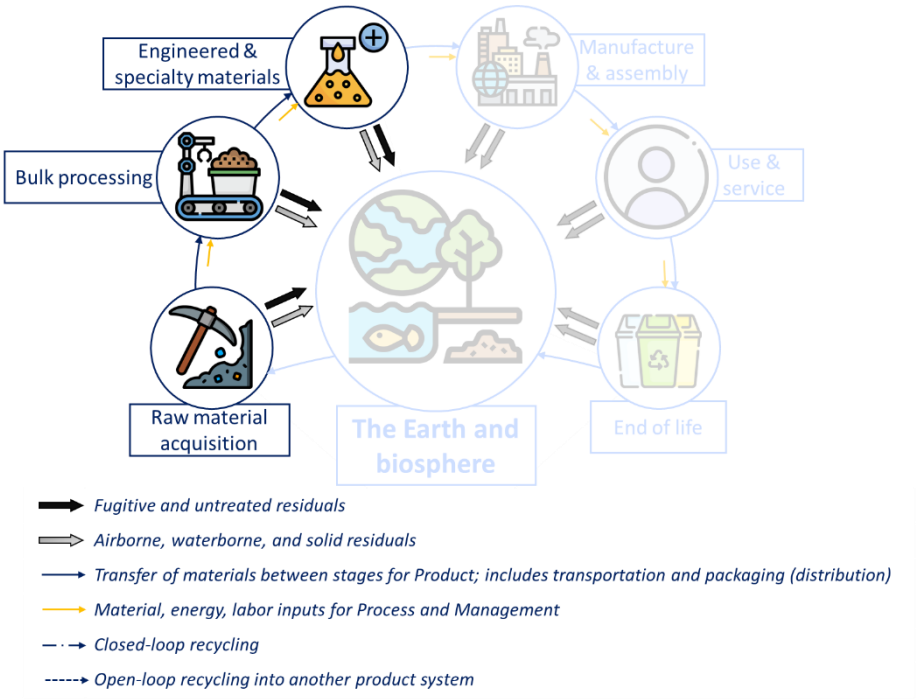


Figure 85 - Considerations to include in mAb LCA, for the raw material step

API

Closely linked to the process of production, the manufacturing of API requires families of raw materials and consumables that can be summarized in the table below.

Table 52 - Non exhaustive list of raw materials required to manufacture a mAb API

Type	Family / role	Example	Reference
Raw material	Chromatography resin	Protein A	
	Feed / Media	Cystein	(Ali et al., 2019)
		Glucose / glutamate / arginine / aspartate / asparagine	(Papathanasiou et al., 2017)
		Amino acids / pyruvic acid / pyridoxine	(Saldanha et al., 2022)
	Media additive	DMSO Potassium acetate Rapamycin Sodium butyrate Dissolved oxygen	(Jain and Kumar, 2008)
	Buffer	Citrate Tartrate Succinate Phosphate	(Zheng and Janis, 2006)
		Histidine	(Saurabh et al., 2022)
	pH adjustment	Hydrochloric acid Sodium hydroxide	(Harbour et al., 1989)
	Water	Water for injection	(Pietrzykowski et al., 2013)
Consumable	Single use assembly	Bag chamber Cable ties Tubes Sensors	(Luu et al., 2022)

Excipients

The assessment allowed us to determine 61 different excipients used in the mAbs. Linked to the preponderant liquid form, 79% of the 239 of the marketed forms contain water for injection. The other main ones include the polysorbate 80 (64%), the L-Histidine (46%), the sucrose (39%) and then the L-Histidine hydrochloride monohydrate (34%). The exhaustive list of excipients is presented in the Appendix 20.

Primary packaging

In this part, a non-exhaustive list of each primary packaging available for the mAbs is suggested. The aim of this part is to highlight main aspects of them. Despite the assessment performed, the literature suggests two other devices possible, especially for mAbs: the needle safety device and the auto-injector (Shire, 2015). The absence of them during the assessment can be explained by the fact that the EMA and the FDA consider the needle safety device as a PFS and the auto-injector as a pen injector.

Table 53 - Main primary packaging available for mAbs

Type	Picture	Picture reference	Repartition within the marketed products

Vial		(Aptar, 2022a)	45%
Pre-filled syringe		(IBSA, 2021)	33%
Pre-filled pen		(MIMS, 2022)	22%
Cartridge		(Aptar, 2022b)	0,4%
Auto-injector		(Roy et al., 2021)	/
Needle safety device		(BD worldwide, 2022)	/

- *Vial*

Vials are composed of a main body, a cap, and a stopper. Usually, the main body is in glass type I, the cap in aluminum or HDPE, and the stopper in an elastomer material (Belboom et al., 2011). Some variation can be found with borosilicate glass or plastic for the main body. But for the mAbs, only glass is used. The table below present main materials possible for the various parts of the vial.

Table 54 – List of materials possible for the vial parts

Part	Main body	Cap	Stopper
Material	Glass Type I Plastic Silicone	Aluminum HDPE	Synthetic rubber Bromobutyl Chlorobutyl Silicone
Reference	(Hibler and Gieseler, 2010; Mercedes Scientific, 2019)	(Belboom et al., 2011)	(Sandle, 2012)

- *Pre-filled syringe (PFS)*

A basic pre-filled syringe is defined as a device with a needle, a barrel, a plunger, and sometimes both syringe cap & needle protector (Ingle and Agarwal, 2014).

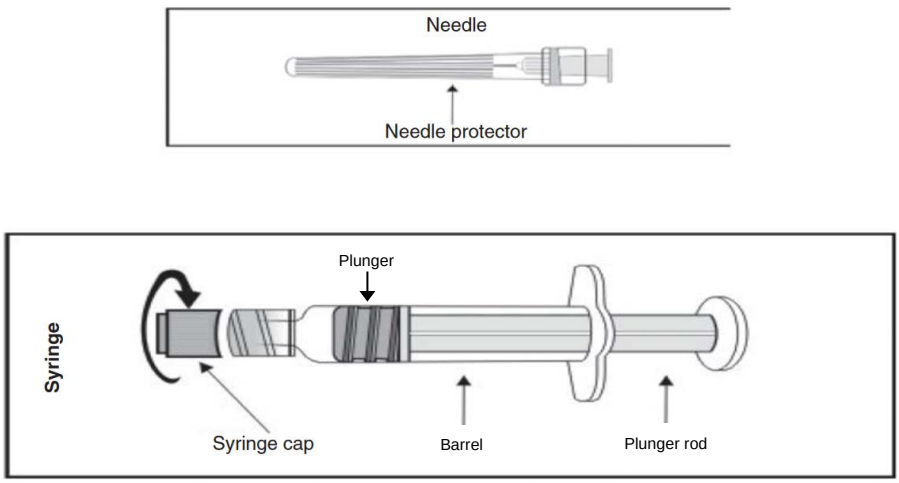


Figure 86 - Design of pre-filled syringe, from Ingle et al. (Ingle and Agarwal, 2014)

The list of materials possible related to each part of the PFS is presented below.

Table 55 – List of materials possible for the PFS parts

Part	Needle	Barrel	Plunger	Plunger rod	Needle protector	Cap
Material	Stainless steel	Glass type I Cyclic olefin copolymer (COC) Cyclo-olefin-polymer (COP) Polypropylene (PP) Polyethylene (PE)	Rubber	Polypropylene (PP)	Natural or synthetic rubber	Elastomeric material
Reference	(Craig, 2018)	(Ishak et al., 2018; Sacha et al., 2010)	(Kiang, 2011)	(European Commission, 2020b; Sacha et al., 2010)	(Sacha et al., 2010)	(Badkar et al., 2011)

- *Pre-filled pen*

Pre-filled pen, also known as pen injectors, are mainly used for insulin. They can be in a single-use format, disposable or reusable (FDA, 2013; Masierek et al., 2022; Thompson and Lange, 2013; Veasey et al., 2021) format. The figure below is an example of the insulin pen SoloStar® components.

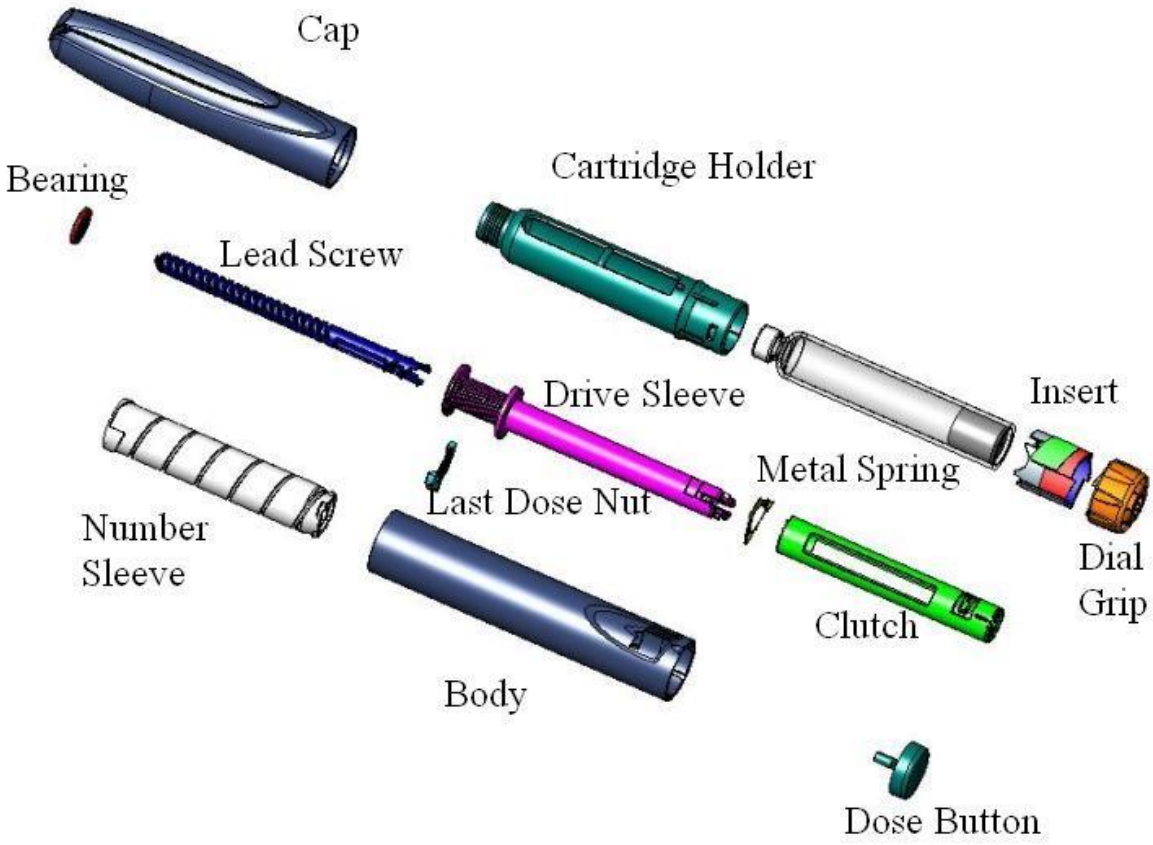


Figure 87 - Exploded view of a pre-filled pen, SoloStar® Pen example, adapted from Mc Arthur (McArthur, 2017)

The list of materials possible related to each part of the pre-filled pen is presented below.

Table 56 - List of materials possible for the pre-filled pen parts

Part	Material
Cap	Polypropylene (PP)
Cartridge holder	Polypropylene (PP)
Insert	Polycarbonate (PC)
Dial grip	Polycarbonate (PC)
Bearing	Polyoxymethylene (POM)
Lead screw	Polybutylene Terephthalate (PBT)
Drive sleeve	Polyoxymethylene (POM)
Metal spring	Stainless steel
Clutch	Polyoxymethylene (POM)
Number sleeve	Polybutylene Terephthalate (PBT)
Body	Polypropylene (PP)
Dosage button	Polybutylene Terephthalate (PBT)

- *Cartridges*

Cartridges are very close to vials. They are composed of a main body, a cap, a stopper.

Figure 88 - Example of cartridges from Stevanato Group (Stevanato Group, 2022a)

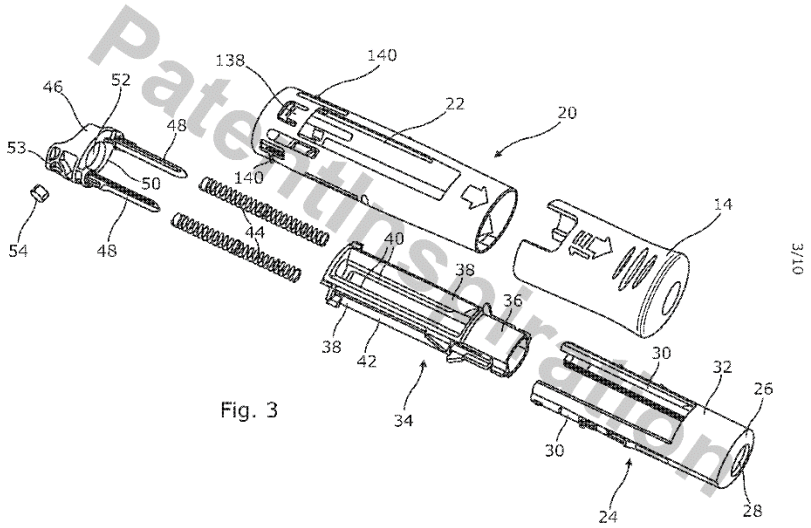
The table below present main materials possible for the different parts of the cartridges.

Table 57 - List of materials possible for the cartridge parts

Part	Main body	Cap / lined cap	Stopper / plunger
Material	Glass Type I Plastic Silicone	Aluminum HDPE Rubber	Synthetic rubber Bromobutyl Chlorobutyl Silicone
Reference	(Hibler and Gieseler, 2010; Mercedes Scientific, 2019; Stevanato Group, 2022a)	(Belboom et al., 2011; Stevanato Group, 2022a)	(Sandle, 2012; Stevanato Group, 2022a)

- *Auto-injector*

Auto-injector are devices that allows patient to self-inject products (Lageat et al., 2021). They are composed of a main body, a pre-filled syringe, and a cap.



Patentinspiration

Figure 89 - Example of an autoinjector, patent US2013310746A1 (Latham, n.d., p. 1)

The table below present main materials possible for the different parts of the autoinjector.

Table 58 - List of materials possible for the cartridge parts

Part	Material / component
Cap	Polypropylene (PP)
Needle	Stainless steel
Pre-filled syringe	See PFS part
Body	Polycarbonate (PC) Polyoxymethylene (POM) Polybutylene Terephthalate (PBT) Polypropylene (PP) Stainless steel (springs)

- *Needle safety device*

A needle safety device can have various forms (Trim, 2004). The one described below is composed of a syringe body, a viewing window, a finger grip, a plunger rod, a needle, a needle shield, and a needle cap. After use, the needle retracts to prevent any accidents. It reuses basically the component of PFS, by adding a mechanism to ensure the safety of the patient.

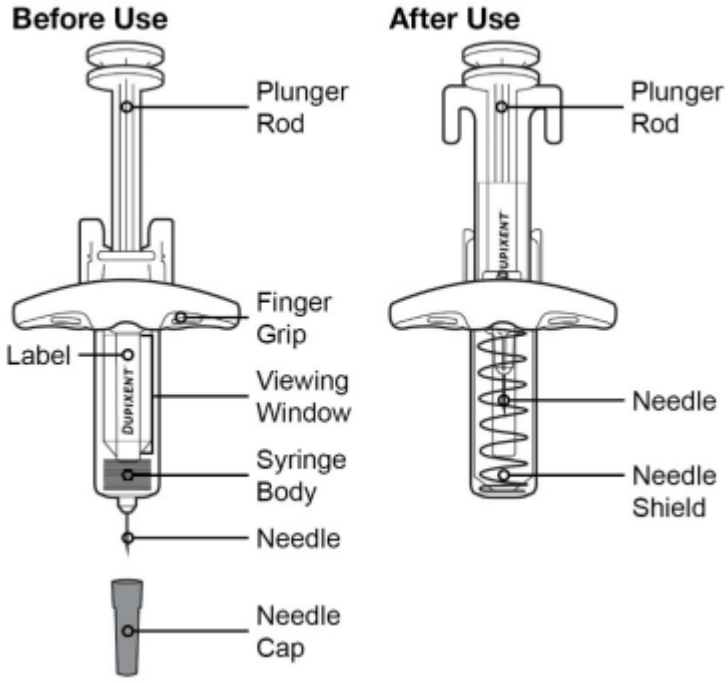


Figure 90 - Parts of a needle safety device, based on Dupixent® (EMA, 2021)

The list of main materials related to each part of the needle safety device is presented below.

Table 59 – List of materials possible for the needle safety device parts

Part	Material	Reference
Needle cap	Natural or synthetic rubber	(Sacha et al., 2010)
Needle	Stainless steel	(Craig, 2018)
Syringe body	Glass type I Cyclic olefin copolymer (COC) Cyclo-olefin-polymer (COP) Polypropylene (PP) Polyethylene (PE)	(Dierick et al., 2017; Ishak et al., 2018; Sacha et al., 2015)
Viewing window	Polymethyl methacrylate	Assumption of LCA expert
Finger grip	Polycarbonate (PC)	(Stevanato Group, 2022b)

	Polypropylene (PP)	
Plunger rod	Polystyrene (PS) Polypropylene (PP)	(European Commission, 2020b; Sacha et al., 2015; Stevanato Group, 2022b)
Label	Polypropylene (PP) Polyethylene (PE) Polyethylene terephthalate (PET)	(Van Noort, 2020)
Needle shield	Stainless steel	Assumption of the authors

Manufacturing

In this part, focus on manufacturing steps who are usually in the perimeter of control of the producer of finished products is done. The API production, and the filling steps, as shown in the figure 91, are presented; from a process perspective.

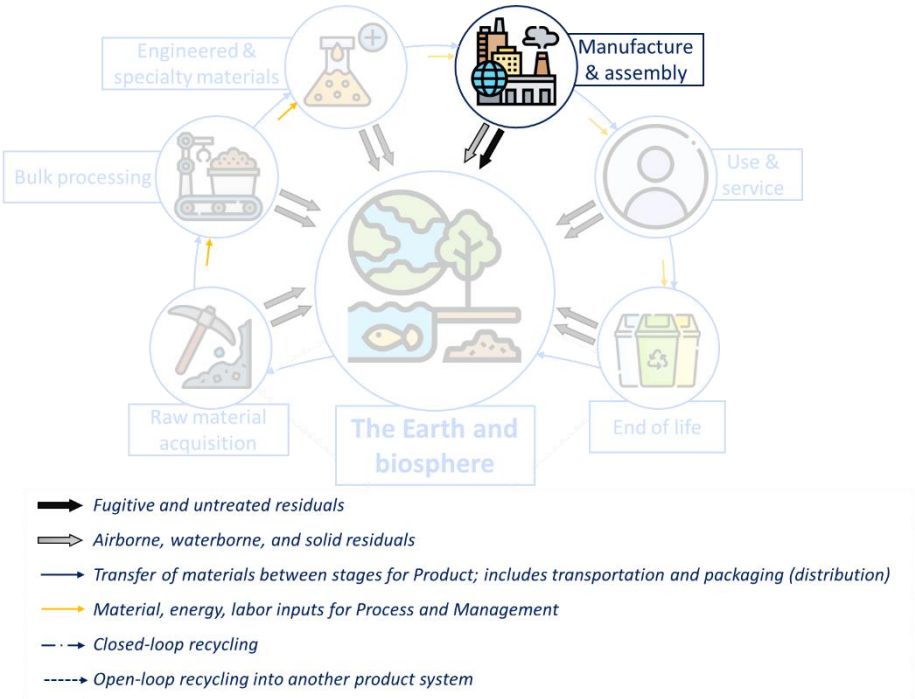


Figure 91 - Considerations to include in mAb LCA, for the manufacture & assembly step

API

The production of Monoclonal Antibody (mAb) is a well-known process, described in the literature (Gronemeyer et al., 2014; Kelley, 2009; Pietrzykowski et al., 2013). It can be segmented with the upstream production and the downstream. The figure 92 present a generic flowchart of mAbs production. The upstream part includes all steps from the cell bank vial to the harvest and centrifugation (Gronemeyer et al., 2014). The downstream include all the remaining steps, the Protein A chromatography, the Anion-exchange chromatography, the Cation-exchange chromatography, the Virus Retentive Filtration, and the UF/DF.

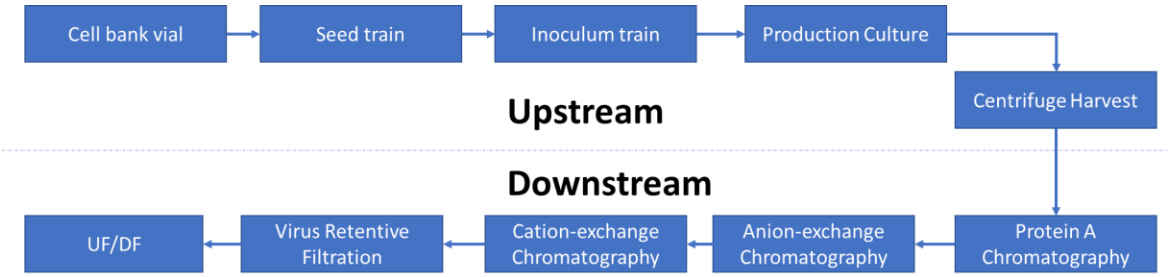


Figure 92 - Generic process flow of mAbs production adapted from Kelley (Kelley, 2009)

If no data related to the energy of the process itself are available, modelization through design process software like Aspen plus ® or SuperPro Designer® can help to fill this gap. The SuperPro Designer® software is providing a template of mAb process that can provide estimation of its energy consumption, which can be adapted to the specific process of the mAb assessed.

The process is not the only contributor in the energy consumption. Due to the regulations and the need to preserve the quality of the rooms, the HVAC systems need to be considered during an LCA of mAb. Depending on if the infrastructure is based on stainless steel or Single Use Technology (SUT), Cleaning In Place (CIP) / Sterilization In Place (SIP) might have an impact within both gases and water consumption (Barbaroux et al., 2020; Budzinski et al., 2022; Pietrzykowski et al., 2013; Rogge et al., 2015). If the process is using SUT, more solid waste than in stainless steel equipment is expected and should be assessed (Budzinski et al., 2022; Ding and Martin, 2010; Jornitz et al., 2012).

The use optimization of chromatography columns and their regeneration are key parameters in mAbs manufacturing (Feidl et al., 2020; Zhou et al., 2019). The regeneration of these columns is therefore relevant to consider in the LCA of such process (e.g.: CIP).

Water for injection (WFI) is used all along the process, to be included in the product but also to clean. The process to generate such water is not neutral and should therefore be included. If no data available, proxies based on the literature can be performed (Cataldo et al., 2020; Pietrzykowski et al., 2013)

$$S_{lb} = \frac{(Q * SA_v * \Delta T * t_{op} * k)}{L_h}$$

Q = heat transfer coefficient (btu*in/ft^2*hr*F)
SA_v = surface area of the vessel (ft^2)
ΔT = temperature difference (F)
t_{op} = operation time per batch (hr)
k = insulation thickness (in)
L_h = latent heat of steam (btu/lb)

Figure 93 - Equation and parameters used to estimate the amount of steam required to generate WFI and maintain a temperature of 80 degrees Celsius by Pietrzykowski (Pietrzykowski et al., 2013)

Filling step

Monoclonal antibodies are medicine products that can only be administrated to patient by injection. As described in figure 83, the galenic forms possible include mainly solution (for infusion or injection) and powder (which are putted then in solution). A filling step is required to put the semi-finished product into its primary packaging.

During the filling step, buffers might be used (Kollár et al., 2020) and are usually composed with the excipient list of the final product. Single Use Assembly can be used during the process to be able to add those buffers (Luu et al., 2022).

Belboom et al. described that the vials in glass need to be *"cleaned and sterilized using steam generated from deionized water before filling. Vial bodies are first washed with deionized water and sent to tunnel oven before being filled with injectable drugs. Then they are closed with vial stopper previously sterilized with steam produced from deionized water and cap is added".* For vials in polymer, those are *"already sterile and cleaned. Filling is realized with a needle passing through the cork followed by laser re-sealing and capping"* (Belboom et al., 2011). In other words, the authors described a consumption of electricity for both systems, with in addition gas and deionized water for the glass vials, and isopropanol, H_2O_2, and sodium hypochlorite for the polymer vials. The cartridges in glass follow the same approach than the glass vials. The sterility of them needs also to be ensured and therefore, cleaning and sterilization might be present during the process. Some guidance were made to set these best practices in the pharmaceutical industry (PDA, 2021, 2013).

Additionally, to that, and like for the API manufacturing, the infrastructure needs to be considered, such as the HVAC systems who guarantee the grade of the production rooms. As the mAbs have usually a range of temperature stability between 2 and 8°C, refrigerated rooms are present to store the production. But this storage might vary with specific products that could be stored at room temperature for a determined range of time.

Freeze-dry

In some cases, mAbs are freeze-dried and putted in a vial. An LCA regarding this process for a monoclonal antibody is available in the literature (Renteria Gamiz et al., 2019b). The authors described this process with several steps, the Loading, the Freezing, the Primary and Secondary Drying, the Stoppering & unloading, the Defrosting, the CIP & SIP, and the Cooling & Drying of the freeze drying, as shown in the figure 94. The authors considered elements such as the steam, the cooling water, the chilling water, the WFI, the deionized water, the superheated water, the compressed air, and the electricity as inputs.

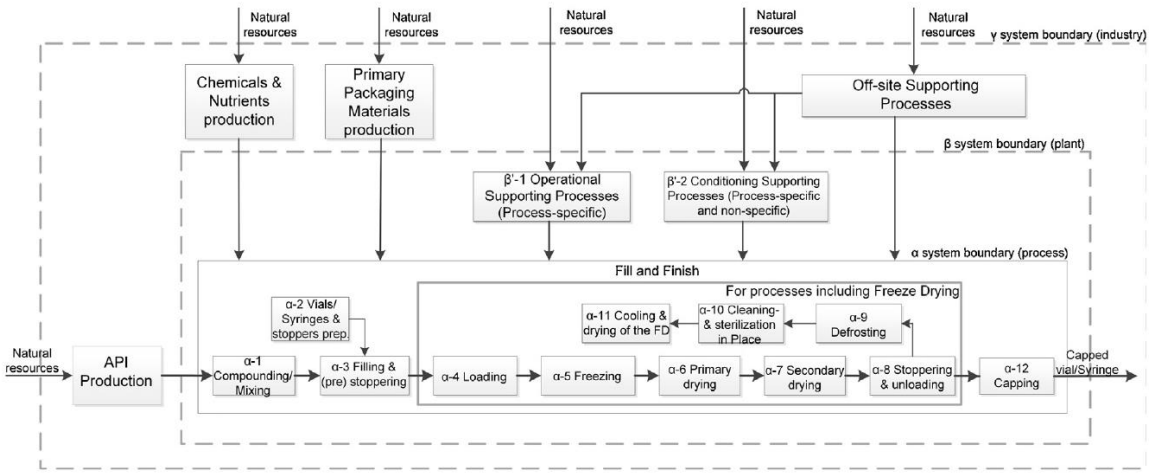


Figure 94 - Basic representation of part of the supply chain of a biopharmaceutical manufacturing plant from Renteria (Renteria Gamiz et al., 2019b)

Distribution

In this part, the distribution step who are usually not fully in the perimeter of control of the producer of finished products is focused. As described in the state of the art (chapter II.4.4), after manufacturing, medicine products are usually sent to a wholesaler, which redistribute then to pharmacies or hospitals. In some cases, the manufacturing site is directly sending shipment to pharmacies or hospitals (chapter II.4.4, figure 23). The mAbs are following the same pathways.

Linked to the stability conditions, mAbs need to be stored at temperature between 2°C and 8°C. It requires a cold supply chain, which is strongly regulated and might be specific for each country (Arrighi et al., 2011; European Commission, 2015; PDA, 2019).

In the cold supply chain, it is possible to distinguish three main types of temperature-controlled transportation (Muspratt, 2018).

Refrigerated vehicles: vehicles that have thermostatically controlled cargo compartments, enabling the temperature range to be maintained

Passive shipping container: storage containers that utilize a combination of insulating materials and electronics to maintain a temperature range.

Active shipping system: large thermostatically controlled cargo containers. On air freight, they are typically powered via internal batteries or an external electrical source and maintain power via large cooling fans and heating mechanisms. Meanwhile, sea freight active shipping systems are generally powered by the ships onboard power supply.

Use

The use of the product will differ regarding the form of the product. The uses in hospitals, through healthcare professionals, and the ones through the patient directly can be identified.

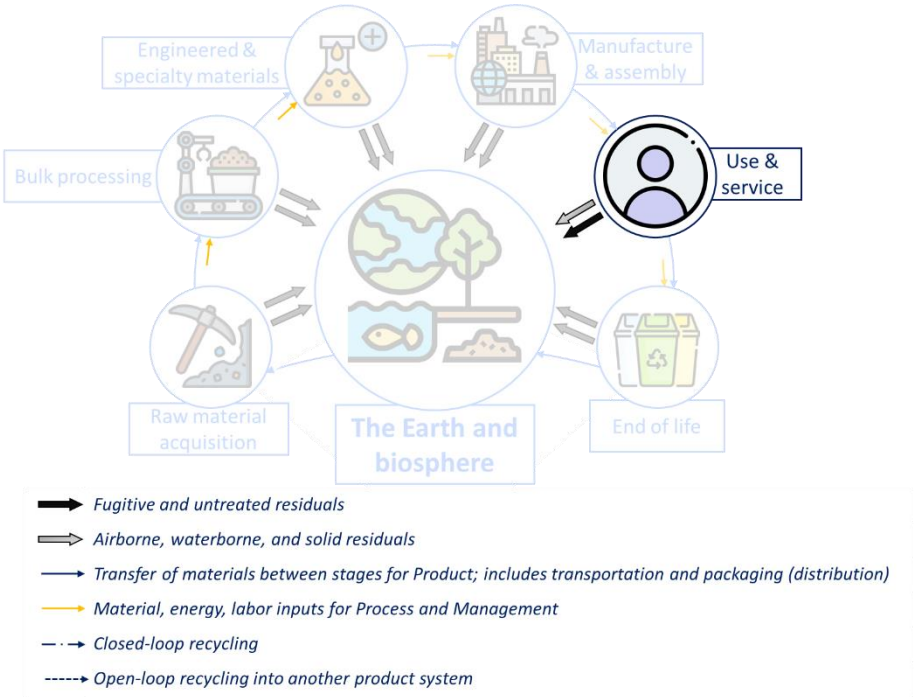


Figure 95 - Considerations to include in mAb LCA, for the use step

When used at hospital, a preparation phase might appear, especially for product in vials. Usually, consumables like syringe, alcohol pad, sharps container, gloves, water for injection are used (Doyle and McCutcheon, 2015; U.S. National Library of Medicine, 2022). These should be considered when assessing the environmental footprint of products. Each mAb in syringe or autoinjector present recommendation of use in their market authorization. In those documents, usage of alcohol pad, and sharps container are recommended.

The transportation of the patient to get their medicines, and the nurse in case of healthcare provided at the patient's home, should be also considered as part of the use phase. The mode of transportation depends on the region and should be adapted accordingly.

End-of-life

For the end of life, pharmaceutical industry considers the API as harmless. As the monoclonal antibodies are proteins, such compounds are usually easily degraded in the environment (Rathore

and Bansal, 2019). However, metabolites might be relevant to study, especially for antibody drug conjugates and their potential of toxicity (Masters et al., 2018; Su and Zhang, 2021).

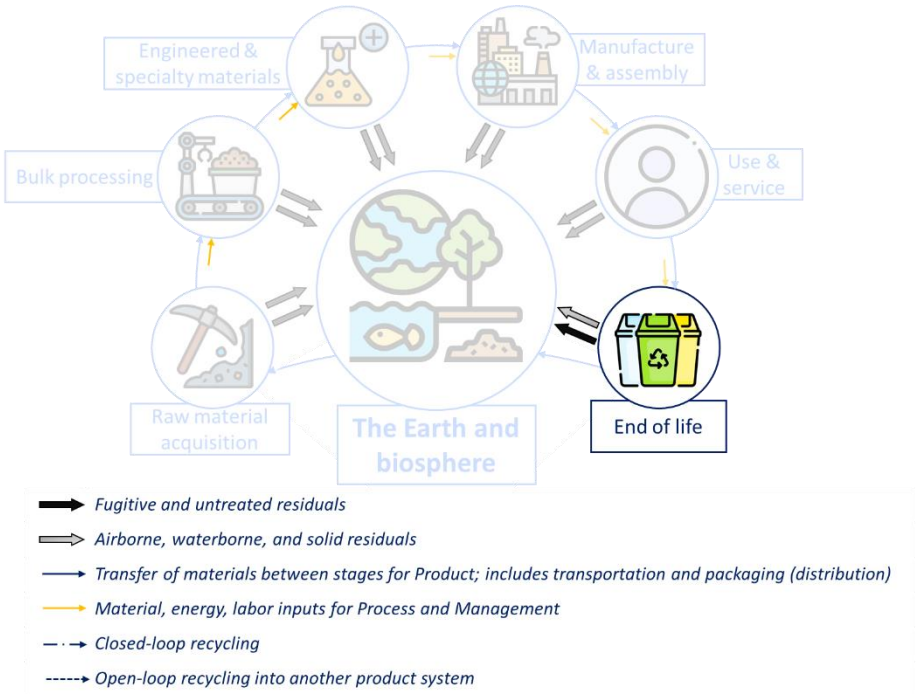


Figure 96 - Considerations to include in mAb LCA, for the end-of-life step

The end of life of the primary, and secondary packaging should be assessed, accordingly to the waste treatment habits of the market considered. If no specific waste stream for unused medicines is in place (e.g.: Cyclamed in France), the common waste stream could be used if no specific data are available (e.g.: OECD reports).

VII.2.3 LCA performed during the PhD

In this part, the detailed Life cycle inventory and the results of the assessment will not be displayed. They are confidential data from the pharmaceutical industry partner of this doctoral thesis. The aim of this part is to describe the methodology who structured the approach.

- *Goal and scope*

To set the goal and scope, the EPAR documentation available in the EMA database was used. Official information in this documentation was gathered to prepare a preliminary report which was used during the kick-off meeting of the LCA project within the pharmaceutical industry partner of the study. With this, the Function, the Functional unit, and the Reference flow (DDD based) of the product assessed was set. As the product might have multiple therapeutic area, the focus on the main indication was made.

However, after the kickoff meeting of the project, the scope of the study was defined as Cradle-to-gate. Adaptation of the project was done by changing these parameters with both API and product focus. The temporality of the assessment was defined as one year of production, in 2021. Despite the COVID-19 situation, the production remained as usual and was therefore representative.

- *Life cycle inventory (LCI)*

During the inventory, primary data were gathered at the production site levels. For both API manufacturing and filling of the product, energy & water consumptions, and emissions (e.g.: waste, wastewater) were collected directly by the production sites. Bill of Materials (BoM) were provided

by Product Life Cycle Managers and production volumes by sites mediator. Those one was either HSE manager, Product portfolio manager or even Supply chain one. To be able to support the data collection, the key success factors were their knowledge regarding the process and their network related to it.

Sample of single use assembly was disassembled at the LCPI. Each part was weighted to be able to address proper weight during the modelization. An amino acid proxy to model the feeds, as the supplier did not provide relevant data to modelize it properly, was used. Exclusion of the Protein A was done, as no reliable data could be found. These examples showed us the complexity to get information from suppliers for complex compounds.

- *Life cycle impact assessment (LCIA)*

As no consensus was made within the pharmaceutical sector, both the Environmental Footprint (EF) and Impact world + were used as LCIA. The first one is recommended by the European commission and, as a French major player of the pharmaceutical industry, this LCIA method was used to suit the European context of the industrial partner. In parallel, Impact world + was chosen, with the perspective in mind to be able to regionalize the assessment.

- *Interpretation*

The interpretation phase was carried out all along the LCA, mainly with an internal LCA expert. Other actors were involved (e.g.: HSE, energy engineer), especially during the LCI, when allocation rules were determined to be able to make proper repartition (e.g.: energy allocation rules).

VII.3 Results

In this part, the establishment of a Product Category Rule (PCR) for mAbs or medicine products were not the aim. However, we aimed to suggest guidance to perform medicines LCA. This part is therefore structured based on the four steps of the LCA methodology.

VII.3.1 Goal and scope

- *Function, Functional unit, and Reference flow*

As described in the state of the art, the notions of Function and Reference flow are not well embraced in the pharmaceutical LCAs available in the literature. Based on the research, the followed guidance is suggested.

Function: the function should describe the main purpose of the product or service, linked to the scope of the study. For Cradle-to-grave assessment, it is strongly recommended to fit the Anatomical Therapeutic Chemical classification (ATC) of the WHO.

Table 60 - Recommendation to set the Function during a pharmaceutical LCA

	Function type	Function example
Cradle-to-gate	• Produce an API • Formulate a product • Produce a product	• Paracetamol production • Freeze-dry production process • Tablet of Doliprane® production
Cradle-to-grave	• Treat symptoms • Heal • Cure • Prevent	• Relief headache • Heal a wound • Cure Hepatitis C • Protect against flu

• Diagnose	• Identify tumor

Functional unit: the functional unit should quantify the function, depending on the scope of the study. For Cradle-to-grave assessment, it is recommended to use the Defined Daily Dose (DDD) of the WHO, when they are defined.

Table 61 - Recommendation to set the Functional unit during a pharmaceutical LCA

Scope	Functional unit type	Example	Pro	Cons
Cradle-to-gate	API focus	1 kg produced	Easy to presents results	Comparability with other APIs with the same therapeutic area not easy
Cradle-to-gate	Product focus	• One batch produced • 100,000 unit produced	Easy to presents results	Comparability with other products with the same therapeutic area not easy
Cradle-to-grave	Product focus	One tablet of product	• Easy to use • Comparison between galenic forms possible	Comparison with other product with same therapeutic area difficult
Cradle-to-grave	Dose focus	• One dose of product • One average dose per intake	Representative of the use	Difficult to compare with chronic treatments
Cradle-to-grave	Duration focus	To protect one person against a disease for one year	Relevant for chronic treatment	Difficult to measure if the treatment duration is inferior to the fixed duration
Cradle-to-grave	Function focus	• Treat symptoms • Heal a patient • Cure a patient • Protect a patient • Diagnose a patient	• Closest to the intrinsic function of medicine • Comparability with other products feasible	Difficult to measure for a chronic treatment

Reference flow: the reference flow should quantify the amount of product or service required to fulfill the functional unit.

Table 62 - Recommendation to set the Reference flow during a pharmaceutical LCA

	Functional unit	Reference flow type	Reference flow example
Cradle-to-gate	Produce 1 kg of API	Manufacturing capacity	X% of the capacity production of the manufacturing site

Cradle-to-gate	100,000 units produced	Manufacturing capacity	X% of the capacity production of the manufacturing site
Cradle-to-grave	To protect one person against a disease for one year	Product / dose focus	One vaccine

- *System boundaries*

Depending on the perimeter of control of the pharmaceutical entity performing the LCA, inclusion of manufacturing steps, such as API manufacturing, can be considered as raw material or manufacturing. The mention of such aspect should be done to avoid any confusion and a flowchart should be generated to clarify it.

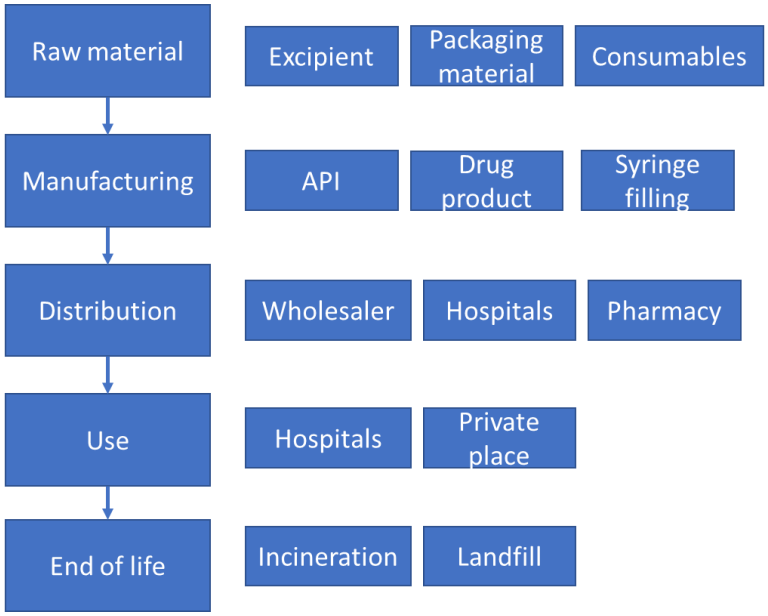


Figure 97 - Example of flowchart presenting the system boundary with elements within each life cycle step

VII.3.2 Life cycle inventory

The Life cycle inventory (LCI) is representing the most time-consuming part of an LCA. Based on the learning experience of this research, a set of guidance in order to optimize the collect of primary data is provided. From a generic perspective, the table 63 is presenting examples of LCI aspects to consider in a pharmaceutical product LCA.

Table 63 – Examples of LCI in a pharmaceutical LCA

Life cycle step	Example of data required	Potential location of data	Potential function to involve
Raw material	• List and quantities of raw materials • Origin of supplier and mode of transportation	• Bill of Materials • ERP systems • Quality documentation	• Quality • Procurement • Supply chain • Product Life Cycle Managers
Manufacturing	• Energy consumption of the site • Energy mix used	• ERP systems • Reporting tools	• Technic • HSE • Supply chain

	• Water consumption • Release of the site (waste, air emission – list & quantities)		• Quality • Product Life Cycle Managers
Distribution	• Manufacturing to Distribution site • Countries destination & ways of transportation • Wholesaler • Pharmacy & hospital destination • Storage condition • Filling rate of truck / plane / boat / train	• ERP systems • Quality documentation	• Supply chain • Product Life Cycle Managers
Use	• Administration of medicine • Habits of patients	• Technical datasheets • EMA of FDA documentation	Marketing Product stewardship
End of life	• Metabolism rate • Unused medicine management of the country • Treatment of patient effluent	• Scientific literature • EMA of FDA documentation • OCDE database	HSE Product stewardship

If no primary data are available, proxies can be used or generated in order to fill the gaps. The PCR proposed by Siegert (Siegert et al., 2019) identified secondary data required and ways to handle the gaps. The possibility to use software like Aspen plus® or SuperPro Designer®, who might help when identifying the energy contribution of the processes is recommended.

The chapter VII.2.2 is presenting aspects of mAbs to consider when performing LCA for such family of products.

VII.3.3 Life cycle impact assessment

As described by Jolliet, the application of the Life cycle impact assessment (LCIA) is quite *"trivial"* and consists of *"multiplying emissions by predefined characterization factors"* (Jolliet et al., 2015). The development of such LCIA methods is in the other hands complex.

From a LCA practitioners' point of view, and especially for the pharmaceutical industry one, no consensus of LCIA method is nowadays made. Therefore, the choice of LCIA method should be done accordingly to the scope of the study and the intended applications of the results. In addition, the choice of indicators should also be done accordingly to those aspects. It can be noted that the use of Midpoint indicators is considered as the most relevant when it comes to display the environmental footprint. However, the communication of such indicators is complex. By using Area of protection, such as illustrated in the figure 98 with the Impact World+ framework, it is possible to ease the communication. But this increases the uncertainty of the results due to the aggregation of indicators.

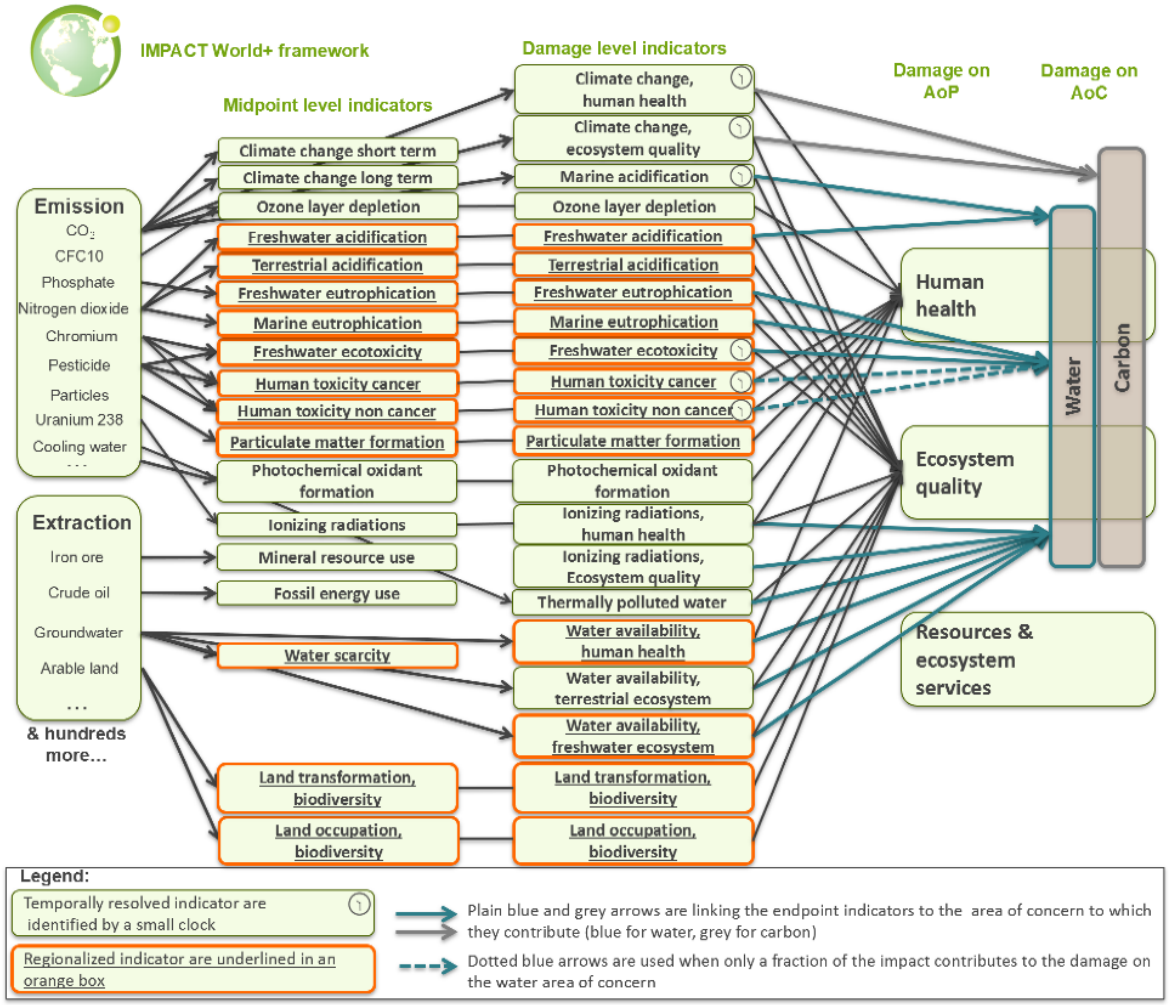


Figure 98 - LCIA method Impact World+ framework, from (Bulle et al., 2019)

VII.3.4 Interpretation

Iterative approach, the interpretation phase appears all along the LCA study. In this part, a summary of main recommendation to optimize this phase is displayed.

Table 64 - Main recommendation for the interpretation, per LCA stage

LCA stage	Interpretation examples	Potential function to involve
Goal & scope	• Market relevant to include in the perimeter (e.g.: from a business perspective) • Steps to exclude (e.g.: identical step in the case of comparative assessment)	Marketing Product Life Cycle Managers
Life cycle inventory	• Proxy of raw material (e.g.: production process to model) • Allocation rules (e.g.: energy used for HVAC, process) • Uncertainty determination (e.g.: pedigree matrix)	• Technical department • HSE • Supply chain • Quality • Product Life Cycle Managers

Life cycle impact assessment	• Non representative inputs Cut off • Uncertainty calculation (e.g.: Monte-Carlo simulation)	• Technical department • HSE • Supply chain • Quality • Product Life Cycle Managers

VII.4 Discussion

During the doctoral thesis, several LCAs were done and specific ones for monoclonal antibodies were performed. During those LCAs, primary data were gathered at manufacturing sites level. However, the usual paradigm of gap of information and the difficulty to identify relevant proxies for several raw materials and consumables appeared. For instance, the Protein A, which is an unavoidable material in the production process of mAb was excluded of the LCA due to the lack of information. Indeed, despite the effort to perform a literature review, the production and the composition of such material was not enough clear to be able to model a proxy. Other elements such as the feeds, were modelized through amino acids. In fact, they are composed with other compounds (e.g.: minerals) but the pharmaceutical industry is facing the difficulty that the suppliers of such materials do not provide their exact composition.

In this chapter, the aim was not to present specific results of the LCA performed. However, recommendations, based on the learning experiences of both LCAs tracked and performed, was proposed. Both specific aspects to deep dive when performing mAbs LCA (chapter VII.2.2) and generic ones (chapter VII.3) were highlighted. The recommendations in chapter VII.3 were based on LCAs performed in parallel of the doctoral thesis. Key points of the LCA, datasets available do not fulfill the needs regarding pharmaceutical products.

The work conducted led us to state that even if LCA guidance can be set, the role / actor of LCA expert should be implemented within the organization. The role of such position should be to guarantee the deployment of the LCA methodology, supervise the datasets construction, and support the evolution of LCA knowledge within the company.

VII.5 Conclusion

Life Cycle Assessment (LCA) is an analytical tool, which the pharmaceutical sector is not yet familiar with. This chapter aimed to set guidance when performing monoclonal antibody LCA, with the target that the pharmaceutical industry can take more ownership of this tool. Through LCAs supervised and performed, guidance was made. Specific for mAbs and more generic ones when conducting medicines product LCA.

As the LCA method is a complex approach, which rely on data availability, the need of both involvement of transversal team and the adoption of a new position within the pharmaceutical organization, the LCA expert are recommended.

VII.6 Summary of chapter 7

The environmental assessment and its knowledge management are key success factors to Eco-designed products.

In this chapter, the Micro level of the integration of eco-design as described by Brones was in the focus. Guidance when performing LCAs, for mAbs and for generic ones was proposed. Those recommendation were built based on LCA performed during the doctoral thesis.

The LCA is not yet mature in the pharmaceutical industry and databases like Ecoinvent are lacking relevant datasets to be able to assess properly the medicine products. With the lack of LCA methodology appropriation from the pharmaceutical industry, this research work led us think that a

new actor is required in the pharmaceutical development: the LCA expert. Indeed, despite the guidance made, the assessment of the environmental footprint remain a complex approach, which required a transversal team not yet familiar with the Eco-design concepts. The LCA expert will be at the interface of each function, to support the environmental assessment and diffuse the LCA mindset across the organization.

Phase 4

Chapter VIII

Contributions and limits

« La science ne connaît qu'une loi : la contribution scientifique »
Bertolt Brech, « La vie de Galilée », 1938

“Science knows only one law: the scientific contribution”
Bertolt Brech, “The Life of Galileo”, 1938

VIII Contributions and limits

The contributions of this research are focusing on making the bridges between academical concepts and the industry. In that sense, both Meso and Micro levels of the Eco-design integration were explored for the pharmaceutical sector to set an Eco-design qualitative framework. This framework aims to be the base of the integration of Eco-design practices for the pharmaceutical sector. Each part of this chapter describes contributions linked to this research which aimed to answer the research question below.

How to foster the Eco-design practices into the New Product Development of medicines in a systemic way?

Part VIII.1.1 focuses on the Eco-design stakeholders' framework for the pharmaceutical industry to manage in order to foster Eco-design practices that is proposed in this research. In part VIII.1.2, a mapping of key steps of the pharmaceutical NPD process to integrate Eco-design is described. From an operational perspective, tools are highlighted in part VIII.2.1 and VIII.2.2, with respectively DEimeter and LCA guidance. The first one aim to track and support the evolution of Eco-design practices within the NPD process while the second tool aim to support environmental assessment through LCA for mAbs.

The contributions summarized in this chapter represents key aspects that the pharmaceutical industry should consider when implementing Eco-design in a systemic way. Limits related to each contribution are presented alongside with them.

VIII.1 Meso level, Eco-design organizational framework for the pharmaceutical industry

The research took its roots with the integration model of Brones. The organizational perspective developed here aimed to explore both the Soft side and the Meso dimensions of his model. The first hypothesis **H.1: "An Eco-design approach can be structured within the current NPD of medicines product"** was explored through the stakeholders' management and the NPD process of medicines.

VIII.1.1 Stakeholders' management

Based on the first hypothesis, a sub-one was identified: H1.1: ***"It is possible to integrate the current environmental expectations of external stakeholders"***. Literature suggests that such elements are key to succeed in the Eco-design journey (Domingo et al., 2015; Keivanpour et al., 2014; Kota et al., 2013).

Medicines products are complex items with a diversity of stakeholders. Through this research, a framework of the stakeholders of medicine products (chapter IV.3.1, figure 52) was settled. In parallel, current trends of the external stakeholders of the pharmaceutical industry regarding their environmental considerations were highlighted (chapter IV.3.2). A framework of the pharmaceutical industry external stakeholders to consider when Eco-design products was defined (chapter IV.3.3, figure 58). A priority mapping of them (chapter IV.3.3, figure 59) was identify in order to support the management of such actors.

Through the research, the hypothesis was not fully validated. Indeed, even if both framework and priority mapping of external stakeholders were made, it was not possible to explore the integration of their current environmental expectations into the development of medicines. However, the contributions presented in this manuscript represent the firsts milestones of this topic.

The adaptation of the pharmaceutical industry to answer the demands of each of its external stakeholders is a key factor of success in the Eco-design perspective. Limits regarding the approach can be summarized as below:

- Despite the effort to include experts with an international perimeter of work, all of them were working in France.

- Even if the experts were not part of the same teams or business unit, they were part of the same pharmaceutical company.
- The framework of stakeholders and its prioritization are intrinsically linked to the type of medicine. An Over the Counter (OTC) medicine can have a business model closer to the cosmetic. In other work, the brand image has a strong influence, and the patient can choose its own medicine. At the opposite, oncology medicine is usually prescribed by physicians and patients do not have strong influence on this decision making. In other words, the prioritization between an OTC and an oncology drug will most likely differ.
- The framework of stakeholders is defined at global level. Specificities of countries were not included. With the National Healthcare Authorities, discrepancies can be expected between territories.

The two last points represent critical aspects that need to be mitigated in future research. Mapping and both evaluation of the level of environmental understanding & expectations of external stakeholders could be fostered. For specific territories (e.g.: Continent / Countries / Regions, types of medicines).

VIII.1.2 Eco-design levers within the pharmaceutical development process

A second sub-hypothesis was formulated: H1.2: ***"It is possible to identify Eco-design levers all along the current NPD process, as well as Eco-designers".*** Even if the literature abound of papers from the pharmaceutical R&D, the study of its process itself is not well explored (Romasanta et al., 2020). The pharmaceutical NPD process is strongly regulated in order to ensure the safety of patients. However, environmental considerations are not made from neither from a lifecycle perspective nor an environmental holistic view.

The development of a medicine product is a long journey with an average around 10 years. Multiple teams intervene during this process and turnover of teams may also represent a challenge. The identification of phases to focus Eco-design effort is therefore key to succeed its implementation.

The research to identify potential Eco-design levers during the development process of medicine products allowed us to make two contributions. The first one is regarding the methodology performed to be able to set the framework proposed in this research. The approach consisted of a qualitative assessment, done by an internal expert of the pharmaceutical industry, with both an LCA result and the detailed list of deliverables during the pharmaceutical NPD process. The methodology is described in the chapter V.2.2. The results of this assessments were compared to the results after practitioners' interviews, in order to highlight the convergence points.

Both qualitative and quantitative approaches of Eco-design can be identified all along the development process of medicines. However, the research emphasis the phases 2a and 2b as the ones with the main Eco-design levers (chapter V.7, figure 65). But it does not mean that Eco-design practices should be avoided at early stage. The research showed that those practices should be adapted in regards of the type of information available. In that sense, the hypothesis H1.2 was validated.

Even if a mapping of Eco-design approaches and potential levers were made, recommendations can be fostered, linked to the limits summarized below.

- The assessment was performed with the NPD process of one specific pharmaceutical company. Even if this process is designed to answer regulatory constraints with defined phases, the "how" companies can handle those might differ.
- The assessment was performed based on a chemical API based medicine and the NPD process of a small molecule drug. Large molecules, such as monoclonal antibody, do not have either the same technologies or the same deliverables within its NPD. Even if Eco-design levers may appear at the same phases, they should not be the same.

Based on the limits identified, future research could foster the identification of Eco-design levers within the NPD process of medicine, in order to optimize the Eco-design appropriation by this sector.

VIII.2 Micro level, Eco-design tools for the pharmaceutical industry

Alongside with the organizational perspective explored previously, the operational aspect of Eco-design was studied in order to validate the overall model of Brones for the pharmaceutical industry. The second hypothesis **H.2: "The adaptation of Eco-design tools can optimize the appropriation of the Eco-design approach in the pharmaceutical sector"** was proposed. During this research, a tool to track the Eco-design practices into the NPD process was developed (the Drug Eco-designed integration meter, DEimeter) and LCAs of mAbs were performed to then set overall guidance when conduction such assessment for this family of products.

VIII.2.1 DEimeter, an Eco-design maturity model for the pharmaceutical industry

The NPD process of medicines are in average around 10 years. During this period, multiple teams and actors are part of the development and turn-over might appear. In the previous part, Eco-design levers within this NPD process were highlighted. To support the integration of Eco-design practices, a sub-hypothesis was proposed: H2.1: ***"It is possible to formalize an Eco-design maturity model for the pharmaceutical sector"***. This sub-hypothesis was explored through the development of an Eco-design maturity tool, specific for the pharmaceutical sector.

Big pharmaceutical companies are complex organizations. An Eco-design maturity model for this sector, the Drug Eco-designed integration meter, which aim to track and support the evolution of the Eco-design practices of the teams was developed.

During this work, two main contributions were made. The first one is to identify the current level of Eco-design understanding and trends of R&D practitioners through a survey. Results showed that most of the pharmaceutical R&D practitioners do not have a clear idea of the concept of Eco-design (chapter VI.3.4, figure 69). However, they consider it as key for the future development (chapter VI.3.4, figure 72). The survey highlighted common constraints already present in the literature such as the lack of resources, trainings, or tools to be able to Eco-design (chapter VI.3.4, figure 73). Potential governance committees were identified in order to set decision making instance where Eco-design should be added (chapter VI.3.4, figure 74).

The second contribution is DEimeter, the tool itself. The overall tool aims to support the "mean" deployed to Eco-design. In that sense, an Eco-design maturity model around two dimensions (the organizational and the operational) was developed (chapter VI.3.3, figure 70). The first dimension aims to support project manager by tracking the practices used during specific phase and by providing guidance to support the practices evolution. The operational dimension focuses on tools, and propose lists of relevant ones, depending on the phase of the development. For instance, Guidance qualitative tools are recommended during the Research phase, while analytical quantitative and semi-quantitative tools appear in the Early development (chapter V.7, figure 65). With this work, the sub-hypothesis H2.1: ***"It is possible to formalize an Eco-design maturity model for the pharmaceutical sector"*** is therefore validated.

Despite the efforts to develop a tool that suit the development phases of the pharmaceutical sector, limits can be highlighted as below:

- Participants of the survey were all part of the same pharmaceutical industry.
- The tool is an Excel file. To be able to track each project of a multinational, another format could be more relevant
- The tool was developed and tested with users. However, it was not used with a real case project.
- The tool was developed to support the generic phases of the pharmaceutical sector (the ones regulatory based). Even if they are common regardless the type of

medicine, details of deliverable might differ and the "how" to handle the development too.

- The user tests highlighted the potential need to address more specific guidance (both organizational dimension and operational) related to functions (e.g.: analytical teams, galenic formulation teams, chemist).

These limits represent opportunities of further research, to confirm the usefulness of DEimeter with real cases and optimize it to maintain its relevancy in the time.

VIII.2.2 Monoclonal antibody LCA guidance

The environmental assessment represents usually the first step of an Eco-design approach. The diversity of products and processes, the international supply chain, raw materials from both chemistry and biotechnology are example that led to a high complexity when it comes to the environmental assessment of medicine products. A second sub-hypothesis H2.2: ***"It is possible to set LCAs guidance for specific pharmaceutical products"*** was proposed.

During this research, Life Cycle Assessments of monoclonal antibodies (mAbs) were performed. The contribution is not the results themselves, but rather the learning experience and a set of guidance to support the next mAbs LCAs that the pharmaceutical industry will perform.

Guidance was made in regards of the LCA methodology and with a Product Category Rule approach. A screening of all the mAbs authorized by the European Medicines Agency (EMA) in Europe and the Food and Drug Administration in the United States was done. The identification of trends regarding technical aspects of them to highlight key aspects to consider when performing a mAb LCA was done.

As the LCA knowledge of the pharmaceutical industry is not high, experts are required to support LCA methodology, datasets construction, and help to diffuse and evolve the related LCA knowledge within the pharmaceutical organization. The sub-hypothesis H2.2: ***"It is possible to set LCAs guidance for specific pharmaceutical products"*** was therefore validated with an additional perspective, the identification a new role key for the Eco-design journey of the pharmaceutical industry: the LCA expert

Linked to the literature available and the LCA that was performed during this, limits of the work are listed below:

- Relations between pharmaceutical industry and suppliers (e.g.: materials, consumables) are complex. Primary data from suppliers were not gathered.
- Database, such as Ecoinvent, do not provide relevant datasets for all materials and consumables (e.g.: protein A).
- No agreement is defined within the pharmaceutical sector to perform Life Cycle Assessment.

These limits are representing key aspects that should be addressed in future research in order to harmonize the environmental assessment of pharmaceutical products and have a relevant start of the Eco-design journey in the pharmaceutical industry.

VIII.3 Summary of the contributions

In order to offer a holistic view of the contributions, they are structured based on the Eco-design integration model of Brones (Brones and Monteiro de Carvalho, 2015), which was one of the spine of the research around the following problematic: ***How to foster the Eco-design practices into the New Product Development of medicines in a systemic way?***

It highlights how the contributions of this research allow to provide answers regarding the problematic formalized (chapter III.1). The first hypothesis **H.1: "An Eco-design approach can be structured within the current NPD of medicines product"** was not fully validated as the sub-hypothesis H1.1: ***"It is possible to integrate the current environmental expectations of external***

stakeholders" was not explored enough. However, the second sub-hypothesis H1.2: ***"It is possible to identify Eco-design levers all along the current NPD process, as well as Eco-designers"*** was validated and a methodology to be able to identify such levers was suggested.

From an operational perspective, this research explored the hypothesis **H.2: "The adaptation of Eco-design tools can optimize the appropriation of the Eco-design approach in the pharmaceutical sector".** The two approaches developed validated this hypothesis. Indeed, through DEimeter, the sub-hypothesis H2.1: ***"It is possible to formalize an Eco-design maturity model for the pharmaceutical sector"*** was not only validated, but a tool was proposed to the R&D practitioners of the pharmaceutical industry in order to track and support the evolution of their Eco-design practices. The second aspect explored through this research was the appropriation of the pharmaceutical industry of the LCAs. As such assessment are complex, the sub-hypothesis H2.2: ***"It is possible to set LCAs guidance for specific pharmaceutical products"*** was made. Even if the pharmaceutical industry has a wide range of products, leading to multiple processes and technologies, some families of medicine products do have the same way of manufacturing. It is the case for the monoclonal Antibodies. LCAs were performed during the research and led us to set overall guidance to perform environmental assessment for such products. Product Category Rules are not yet available for all medicine products, but this guidance show that it is possible to build specific elements that will contribute to the overall picture. The sub-hypothesis H2.2 is therefore validated. Moreover, due to the lack of datasets available, the work done emphasis the need of the LCA expert within the pharmaceutical industry. Such expert is strongly recommended to support the development of datasets & the data collection, modelize in software like SimaPro, and interpret results.

Moreover, an update of the model of Brones is proposed. Based on my observations, the Macro level and the Micro level do also have interactions that need to be considered. Indeed, for instance, the strategical choice to target a country market regarding another will impact the way to perform an LCA. From an operational point of view with the datasets used but also from a methodological perspective where the LCIA choice must be relevant for the market targeted. In that sense, a proposition to add two arrows which links the Macro and Micro level, as shown in the figure 97 is set.

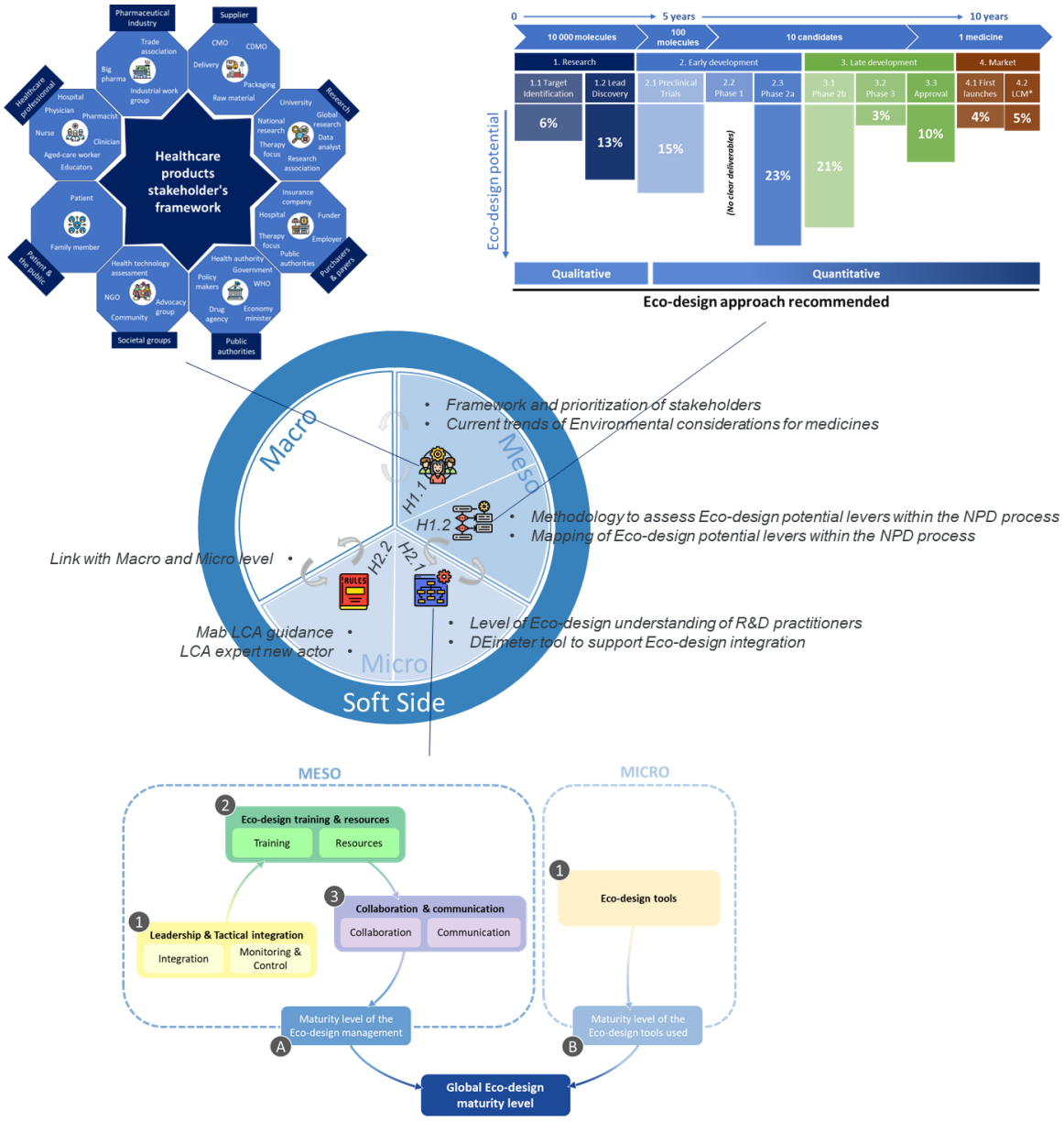


Figure 99 - Summary of the contributions, structured with the Eco-design integration model adapted from Brones

Phase 4

Chapter IX

Conclusion and perspectives

« Tout ce que je sais, c'est que je ne sais rien »
Socrate, Platon, « Ménon »

“All I know is that I know nothing”
Socrate, Platon, « Ménon »

IX Conclusion and perspectives

This chapter aims to present an overview of the research presented in this manuscript. A first part will present a conclusion, by exposing the structure of the research and presenting the results of each contribution related to the hypothesis. Finally, perspectives will be displayed to open the ways of future research directions, linked to the doctoral thesis.

IX.1 Conclusion

In this part, the structure of the research will be reminded to then conclude about the contributions in regards of the related hypotheses.

Through the state of the art presented in chapter II, current environmental considerations of the pharmaceutical industry were exposed with main limits and constraints. The lack of Eco-design appropriation with the holistic perspective was perceivable.

- *Problematic*

The problematic formalized in this doctoral thesis target the implementation of the Eco-design approach in the pharmaceutical R&D and was therefore formalized as such:

"How to foster the Eco-design practices into the New Product Development of medicines in a systemic way?"

The formalization of the hypotheses took their essences based on the observations below:

- Current environmental aspects of medicines are based on a Cradle-to-gate mindset
- No holistic environmental aspects are studied during the development of medicines
- Eco-design mindset and approaches are not implemented in the pharmaceutical sector

Those observations led us to define two hypotheses, one based on the organizational axe and another one on the operational axe.

- *Hypothesis 1*

Based on the observations from the state of the art, ***"an Eco-design approach can be structured within the current NPD of medicines product"*** was built as the first hypothesis to focus on the organizational perspective.

To ensure a proper integration of Eco-design, the interest of external stakeholders regarding such approach was questioned. The experimentation presented in chapter IV showed both mapping of the external stakeholders and the trends of their current interest. The mapping of the prioritization by internal experts of a pharmaceutical company partially validated the hypothesis H1.1 *"it is possible to integrate the current environmental expectations of external stakeholders"*. Indeed, this framework emphasis the fact that the environmental considerations of such stakeholders need to be included, but the identification of the mechanism to be able to integrate them was not explored.

As the development of medicine is a long journey, the prioritization of when concentrate effort to Eco-design medicine products seemed key. The second sub-hypothesis H1.2 ***"it is possible to identify Eco-design levers all along the current NPD process, as well as Eco-designers"*** was fulfilled with the experimentation presented in chapter V.

- *Hypothesis 2*

The operational perspective was treated in this doctoral thesis around the second hypothesis ***"The adaptation of Eco-design tools can optimize the appropriation of the Eco-design approach in the pharmaceutical sector"***.

Linked to the Eco-design levers identified during the NPD process and described in the chapter V, the sub-hypothesis H2.1: ***"It is possible to formalize an Eco-design maturity model for the pharmaceutical sector"***. was proposed. The development of DEimeter validated this hypothesis and the process of development allowed us to emphasis the need of trainings, tools and resources of R&D practitioners to enable a systemic approach of Eco-design.

Key factor of an Eco-design approach, the capacity of teams to assess the environmental footprint of their products or service is essential. The last sub-hypothesis was built with this in mind: H2.2: ***"It is possible to set LCAs guidance for specific pharmaceutical products"***. The work performed allowed the partial validation of this statement. Indeed, through guidance for mAbs, it is possible to set guidance for this family of products. However, mAbs presents the specificity to have a production process quite similar from one to another. Therefore, guidance to perform LCA are relevant to set for such family. It does not mean that it could not be the case for the other families of medicines, but it is not representative of the complexity that will require the development of other guides. Additionally, to that, this research emphasis the need of a new actor within the development of medicine: the LCA expert. The role of such position should be to guarantee the deployment of the LCA methodology, supervise the datasets construction, and support the evolution of LCA knowledge within the company.

Even if the sub-hypotheses H1.1 and H2.2 were partially validated, this research was able to demonstrate that, to be able to reach a systemic approach of Eco-design, the pharmaceutical industry should focus on both organization and operational axes, by supporting the integration of Eco-design in relevant phases of development with proper tools & methods.

IX.2 Perspectives

As any research, the work presents limits highlighted in chapter VIII. These limits open research perspectives to foster aspects that were not possible to explore, and other fields of research will be exposed to broaden the scope of the work.

- *Own contributions perspectives*

Table 65 - Summary of perspectives linked to the contributions of this doctoral thesis

Contribution	Perspectives
External stakeholders' framework	• Set framework adapted to specific geographic scope (Continent / country / region) • Set framework and prioritization adapted to specific therapeutic families • Sensibilize / train external stakeholders regarding environmental footprint of medicines • Explore the mechanism to switch from Environmental expectations of external stakeholders to requirements of development
Eco-design levers within the pharmaceutical development process	• Explore the Eco-design potential levers framework for large molecules process • Foster the mapping with other big pharma • Foster the mapping with smaller companies

DEimeter	• Adapt the tool to specific functions • Adapt the tool to specific medicines • Test the tool in real cases
Pharmaceutical LCA guidance	• Explore the other Lifecycle aspects of the mAbs (e.g.: vial packaging) • Set Product Category Rules adapted to the pharmaceutical products (e.g.: per family of API, formulation technologies) • Develop datasets relevant for the pharmaceutical sector (e.g.: raw material such as Protein A; processes)

- *Eco-design integration model perspectives*

In the part VI and through DEimeter, levels of Eco-design maturity are suggested. They are implicitly considering the Meso level and the Micro one. In order to foster the integration of Eco-design, levels could be formalized for each dimension, including the Macro and the Soft side. The perspectives identified in table 65 are summarized in a suggested Eco-design framework integration model with different levels in the figure below where, for each dimension, darkest colors are representing the highest level (5) and clearer colors are representing the lowest level (1).

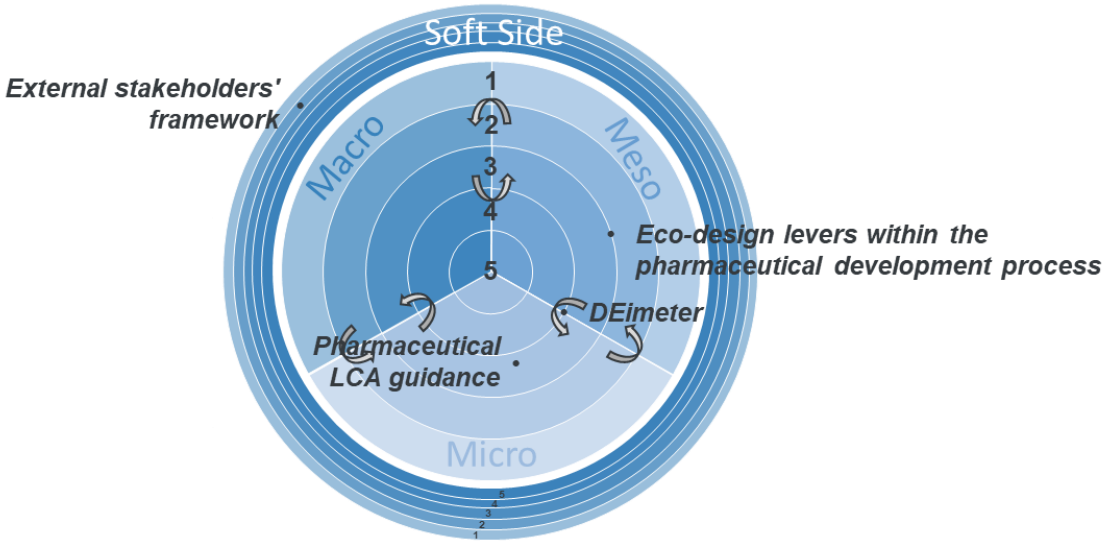


Figure 100 - Eco-design integration model suggested for further research with the perspectives linked to this thesis

The definition of the different levels of each dimension is a perspective of research that could be fostered with a sectorial approach. Indeed, by considering the level 5 as the highest, specificities to consider will most likely appear such as the optimization modules for targeted products in the Micro level. For the Macro level, questions regarding how to implement the environmental aspects into the business model of the different sectors could be raised at level 5. Appendix 21 presents suggestions of the levels, for each dimension, that could be formalized in further research.

- *Environmental sustainability of the pharmaceutical industry perspectives*

In this part, several questions raised during this doctoral thesis are summarized and are structured through different axes.

- ***Axe 1: Eco-design strategy***

The Eco-design strategy, or the Macro level in the Brones model, was not directly in the scope. However, this level is closely linked to the Meso one. By working on the Meso level, questions around the Macro one was raised and several perspectives appeared.

How to structure a global Eco-design strategy in line with the different Business Units of a multinational company?
How to deploy a global Eco-design strategy within all the management layers of a multinational company?
How the Eco-design Macro level interact with the Micro level?
How relevant stakeholders of the value chain of the medicine products can collaborate to foster Eco-design such products?

- ***Axe 2: LCA & pharmaceutical industry***

As demonstrated in this doctoral thesis, the pharmaceutical industry is lacking maturity regarding the LCA approach. Several questions and perspectives can be raised to increase its maturity, and surprisingly, the pharmaceutical industry could also contribute to the LCA methodology in a global perspective.

Develop raw material and processes datasets for medicines products.
How to foster the LCA metrics within the stakeholders of healthcare products?
How the methodologies to determine the eco-toxicity of medicines could improve the models based on USETOX, usually used in the LCA?

- ***Axe 3: Environmental burden and societal contribution of medicines***

Medicines products provide treatments to heal, cure, protect or diagnosis diseases. There are few doubts regarding the societal roles of such products. However, ethical paradox appears when such products are factually polluting but savings lives at the same time. As previously, those thoughts led us to the questions below:

Could a balance societal benefit vs environmental burden could be set for medicine products?
How a responsible consumption of medicine could be fostered?

- ***Axe 4: Circular economy & pharmaceutical industry***

The Circular Economy (CE) is facing a growing interest both in the scientific literature and the societal communities. Since decades, the pharmaceutical industry already performed CE approaches, especially at site manufacturing (e.g.: solvent reusage / recycling). However, and unlike other industries, the notion of CE for the product itself is singular for a medicine product. It raises several questions as listed below:

What do we consider when we talk about CE of pharmaceutical products?
Which close and open loops could be fostered in the pharmaceutical sector?
How can the Eco-design approach foster the CE in the pharmaceutical sector?

- ***Axe 5: Design for Sustainability & Healthcare***

The Eco-design is not the only approach when it comes to Design for Sustainability (DfS), even when we focus only on the environmental perspective of the Sustainability. The intrinsic role of medicine product is to maintain the well-being and health of population. When we think about these intrinsic functions and try to have a step back with the DfS framework of Ceschin, opportunities might appear through the Product-service system, the Spatio-social, and the Socio-technical system levels approaches, by thinking more broadly with the Healthcare systems.

How can the DfS approaches reshape the Healthcare systems?

- *Perspectives temporality*

All the perspectives mentioned above do not have the same impact, neither workload. An overall temporality of them can be set and is proposed below.

Table 66 - Summary of the perspectives with their temporalities

Topic	Short term	Mid-term	Long term
Perspectives directly related to the contributions			
External stakeholder's framework	• Set framework adapted to specific geographic scope (Continent / country / region) • Set framework and prioritization adapted to specific therapeutic families • Sensibilize / train external stakeholders regarding environmental footprint of medicines	• Explore the mechanism to switch from Environmental expectations of external stakeholders to requirements of development • Foster the Eco-design partnerships with actors of the whole value chain of medicine	• Include external stakeholders in the Eco-design process
Eco-design levers within the pharmaceutical development process	• Explore the Eco-design potential levers framework for large molecules process	• Foster the mapping with other big pharma • Foster the mapping with smaller companies	• Add regulatory Eco-design deliverable in the pharmaceutical NPD process
DEimeter	• Test the tool in real case	• Adapt the tool for specific functions • Adapt the tool for specific medicines	• Add a module to optimize resource allocation during project
Pharmaceutical LCA guidance	• Explore the other Lifecycle aspects of the Mabs (e.g.: vial packaging, use and end of life)	• Make available simplified LCA tool for non-experts • Develop datasets specific for the pharmaceutical sector	• Develop a PCR for all medicine products
Eco-design integration model	• Formalize interaction between Micro and Macro level	• Explore and formalize the levels of each dimension	• Foster the model for the other sectors
Perspectives indirectly related to the contributions			

Axe 1: strategy	• Explore link between global strategy to Business unit	• Explore the mechanism to diffuse global strategy within all management layers	• Explore the mechanism to foster collaboration with relevant external stakeholders
Axe 2: LCA	• Explore the manner to diffuse and reinforce the appropriation of the LCA	• Develop datasets specific for the pharmaceutical sector	• Improve LCA ecotoxicity calculation, based on learning experience and approaches from pharma
Axe 3: Environmental and societal balance	• Foster the proper use of medicine practices	• Develop unused medicine program to mitigate end of life	• Develop an environmental burden / societal benefit balance
Axe 4: Circular economy	• Formalize the circular economy concept for the pharmaceutical sector	• Foster the partnerships with stakeholders of the value chain	• Explore the role of Eco-design in the pharmaceutical circular economy • Set a circular economy transition model for the pharmaceutical industry
Axe 5: DfS & healthcare	• Include social perspective in the development of products	• Diffuse other DfS approaches in the development process	• Explore the mechanism to reshape healthcare through DfS approaches

IX.3 Publications linked to the doctoral thesis

The results of the research presented in this manuscript allowed the scientific publications and communications listed below.

- *International journal*

Luu, D.-N., Gachet, H., Maier, C.-J., Maranzana, N., Aoussat, A., 2022. Eco-design and medicine: Opportunities to implement eco-design in the pharmaceutical R&D process. Journal of Cleaner Production 132785.

- *International conference*

Luu, D.-N., Maier, C.-J., Gachet, H., Maranzana, N., Aoussat, A., 2021. Integration of environmental aspects into NPD process: a framework for the Pharmaceutical industry. Presented at the IFIP 18th International Conference on Product Lifecycle Management, p. 14.

- *National conference*

Luu, D.-N., Gachet, H., Maranzana, N., Kozderka, M., Aoussat, A., 2020. Eco-conception et médicament : Quel périmètre pour un développement méthodologique. Presented at the e CONFERE 2020 - 27ème colloque des Sciences de la conception et de l'innovation.

Luu, D.-N., Maier, C.-J., Maranzana, N., Aoussat, A., 2021. Ecodesign & medicine products: the pharmaceutical sector complexity. Presented at the 17e Colloque National S-mart, pp. 71–76.

- *Other presentation*

Luu, D.-N., Maier, C.-J., 2022. Sustainability in companies (Sanofi) & Eco-design. MolBio Symposium, Sustainability in Science. Heidelberg University, Germany.

In addition of the publications and communications mentioned above, two papers are already written and ready for submission:

Luu, D.-N., Journel, R., Maier, C.-J., Maranzana, N., Aoussat, A., 2023. Eco-Design and medicine: a stakeholders' framework to foster eco-designed drugs.

- Journal targeted: Corporate Social Responsibility and Environmental Management

Luu, D.-N., Massot, S., Maier, C.-J., Maranzana, N., Aoussat, A., 2023. DEimeter: a proposition of an Eco-design maturity model to foster Eco-design integration in the Pharmaceutical R&D.

- Journal targeted: International Journal of Sustainable Engineering

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Appendix

Appendix 1

List of PhDs of the LCPI since 2000

Author	Year	Title
Marc JANIN	2000	Eco-design approach in business: a challenge, building consistency between tools and processes
Fabrice MATHIEUX	2002	Contribution to the integration of end-of-life recovery from the design of a product: a method based on the multi-criteria evaluation of the recyclability of the product and on the identification of its weak design points
Alain CORNIER	2004	Development of a material removal model by granulation using high pressure water jet: application to tire dismantling
Stéphane LE POCHAT	2005	Integration of eco-design in SMEs: proposal of a method of appropriation of know-how for the environmental design of products
Nizar HAOUES	2006	Contribution to the integration of disassembly and recycling constraints from the first phases of product design
Virginie HYERARD	2007	Proposal of recommendations for the efficient integration of Industrial Design in technocentric design: Application to the innovative helicopter
El Arbi HASSANI	2007	Quality in research: proposal for a joint development of quality and research processes
Erwan HARSCOET	2007	Development of environmental accounting oriented towards value creation: application to pollution prevention investment
Céline MOUGENOT	2008	Modeling the exploration phase of the product design process, for increased creativity
Stéphanie IBANEZ	2008	Design of a balanced performance model: innovative levers in terms of people management
Yann LEROY	2009	Development of a methodology for making environmental decisions more reliable in the context of life cycle analyzes based on the analysis and management of uncertainties on inventory data
Carole MAUDET-CHARBUILLET	2009	Proposal of tools and approach for the integration of plastics recycling sectors in the automotive supply chain
Wassim DAOUD	2009	Development of an integrated management system for the eco-design of medium voltage electrical equipment
Brigitte LANGEVIN	2010	Considering the variability of field emissions in the life cycle analysis of agricultural systems: application to slurry spreading
Nathalie LAHONDE	2010	Optimization of the design process: proposal of a method selection model for decision support
Aurélia CHEVALIER	2010	How to design a protocol for the application of laser and nanogel technologies for the conservation/restoration of paintings on canvas
Héon SONG	2010	Modeling multidisciplinary creative activity in user-centered architectural design: application to emergency housing
Simone DA VEIGA	2010	Proposal for a multi-project risk management method: application to Institut Curie - Hospital
Anne BERANGER	2011	Promoting the creation of new objects through materials and processes within a traditional house with a strong identity: the case of Hermès

Frédéric SEGONDS	2011	Contribution to the integration of a collaborative environment in the upstream design of products
Lorraine BERGERET	2011	Innovation and design: contribution of design to the expansion of the identity of materials
Julien NELSON	2011	Contribution to the prospective analysis of uses in innovation projects
Jieun KIM	2011	Modeling of cognitive and affective processes in upstream design: application to mental categorization operations present during the generative phases
Léonard CHEMINEAU	2011	Development of an eco-design method based on the modeling and evaluation of recovery channels: application to the automotive sector
Marion PRINCAUD	2011	Development of an environmental decision support tool based on life cycle analysis integrated into the design process
Ornella PLOS	2011	Innovate for and through disability. Product design methodology adapted to niche markets: application to the motor disability market.
Estelle COSTES	2012	Consideration of tactile perception in the design of representations of works of art for people with visual disabilities
Kerstin BONGARD-BLANCHY	2013	User experience in upstream design: from idea generation to evaluation
Sébastien VOISEMBERT	2013	Design and modeling of an ultralight robotic arm
Virginie FORTINEAU	2013	Contribution to an ontological modeling of information throughout the product life cycle
Ioana Cristina OCNARESCU	2013	The aesthetic experience and the culture of innovation: the aesthetic experience of designers and the influence of design for a culture of innovation
Marc TRELA	2013	Optimization of innovation performance: an approach combining technical inventiveness and the search for commercial success
Vincent RIEUF	2013	Modeling and computation of the trend analysis process via virtual reality technology
Tatiana Margarita HERNANDEZ RICO	2013	The "how" of entrepreneurship: towards a useful roadmap of critical inputs and outputs of business creation
Francis RASAMOELINA	2014	Development of a user model for linking Kansei and Eco-design
Alain FERCOQ	2014	Contribution to the modeling of lean green integration applied to waste management for a balanced performance (economic, environmental, social)
Elisabeth MARIS-FROELICH	2014	Eco-design by a Multicriteria Approach of a Polymer/Tracers/Detector System for automated sorting by UV-VIS fluorescence spectrometry to increase the recyclability of products
Alexandre GENTNER	2014	Definition and representation of intentions related to the user experience in the upstream phase of the product design process
Gaëtan PATRY	2014	Keys to technical and economic progress of lithium-ion batteries for automobile traction
Romain LORENTZ	2014	Formalization of a design and innovation model in the field of bio-industries: case of clay particles
Mathieu BAUDIN	2014	Driving Complexity: Using DSM and Allen's Interval Algebra for Collaborative Planning

Yacine BENABID	2014	Contribution to improving the process of designing innovative products: Development of tools to help choose processes
Jessy BARRE	2015	Towards new tools for anticipating user needs: methodological contributions for prospective ergonomics
Pathum BILA DEROUSSY	2015	Systemic approach to creativity: Tools and methods to address complexity in upstream design
Djamel YOUSNADJ	2015	Formalization of a model to improve the sustainability of a portfolio of luxury packaging and innovation: Structuring and Structural Dimensions
Paula CARDOSO GONCALVES	2015	The integration of users in the innovation process for the design of new luxury products
Malte SCHOFER	2015	Processes and methods for solving interdisciplinary problems and integrating technologies in knowledge-based fields
Anne SOUZA MARTINS	2016	Proposal of a methodology that integrates cultural aspects in the implementation of Lean Management: Comparative study France-Brazil
Floriane LAVERNE	2016	Designing with Additive Manufacturing: A proposal for the upstream integration of knowledge relating to a technological innovation
Baptiste HERVE	2016	Service design in product-oriented companies based on data valuation systems
Asma TALHI	2016	Proposal of a unified Cloud Manufacturing modeling and implementation methodology, based on inference ontologies
Ovidiu Mihai BALAN	2016	Technical-economic and environmental assessment of methane storage of renewable energies, in the specific conditions of Romania and in a generic European case
Oscar RAMIREZ SERRANO	2016	Optimization and management of the medicalex innovation process: application to custom-made orthopedic implants
Everton Sidnei AMARAL DA SILVA	2016	Design, Technology and Perception: Connecting sensory, semantic and emotional design with texture and materials
Pierre-Emmanuel FAYEMI	2016	Innovation through bio-inspired design: proposal of a model structuring biomimetic methods and formalization of a knowledge transfer tool
Théo MAHUT	2017	Development of a Kansei methodology through physical and digital interactions
Anne-Lise RIAS	2017	creativity by and for additive manufacturing: proposal of a tooled methodology
Etienne BOISSEAU	2017	Open-Design. Modeling the open design process in the development of tangible products
Sara AID	2017	Study of the miscibility of polymers by the grain coalescence method for the recycling of WEEE by rotational molding
Thibault VALLET	2017	Design of a drug acceptability assessment tool
Baptiste PICLET	2017	Product, process and organization innovation in the field of orthopedics
Brahim MAHIDDINI	2019	Contribution to the improvement of the preliminary design of a product: Approach based on the implementation of optimization techniques
Edouard TAPISSIER	2019	Design of a knowledge management system for an SME

Kévin AUDOUX	2019	Proposal of a multi-domain evaluation process to improve product design
Anthony BRANDY	2019	optimization of a design process by quantification of use
Cédric AVANZINI	2020	Development and implementation of a collaborative design methodology on perceived quality by integrating sensory perception analysis
ALAA Elboudali	2020	The development of a design tool for a virtual store based on the behavioral experience of the consumer
Eliot Graeff	2020	bio-inspired innovation: modeling of an interdisciplinary tooled biomimetic design process and integration of a new actor, the Biomimetician
Jean-Thomas CORNELIS	2021	Modeling of an organization re-design approach with integration of the consistency factor.
Chawki EL ZANT	2021	Industry 4.0 process – Which model for a successful integration
Anneline LETARD	2021	Contribution to the development of the methodological framework of biomimetic design: integration of the expertise of profiles trained in Design to promote the deployment of the approach in design and innovation practices
Jean-Marc VASNIER	2021	Formalization of a prescriptive model for deploying an optimal value creation strategy. Application to the field of SMEs
Clara GANDREZ	2022	Behavioral model for identifying limit situations in autonomous driving
Armand HUET	2022	Proposal of an intelligent assistant dedicated to design rules for the manufacturing industry
Arava SANDFORD	2022	Proposal for a method for designing and managing inter-subsidiary collaborative structures: Application to the creation of innovative offers for the territories of tomorrow.
Armand LANG	2022	Methodology for integrating additive manufacturing as a source of creativity for the manufacturing industry
Bouha EL MOUSTAPHA	2023	Formulation and study of a thermal energy accumulator geopolymer in the context of the eco-construction of buildings

Appendix 2

Perimeter of published pharmaceutical LCA assessed in the manuscript

Reference	Raw material	Manufacturing										Distribution	Use	End of life
		API				Galenic form		Packaging / device			Waste			
		Chemical	mAb	Vaccine	Enzyme	Tablet	Freeze dry	Blister	Inhaler	Vial				
Jonge 2003	X	X									X			
Bruggink 2006	X	X									X			
Curzons 2007	X	X									X			
(Nielsen et al., 2007)	X	X									X			
Henderson 2008	X	X									X			
Kim 2009	X				X									
Ponder	X	X									X			
Raymond 2010											X			
Wernet 2010	X	X									X			
Belboom 2011										X	X	X	X	X
Pfizer 2011	X			X							X			
Cook 2012														X
Köhler 2012														X
De Soete 2013						X								
Pietrzykowski 2013	X		X								X			
Brunet 2014		X									X			
Ott 2014		X									X			
Cespi 2015	X	X									X			
Elzanfaly 2016											X			
Bunnak 2016	X		X								X			
Lee 2016	X	X									X			

McAlister 2016	X	X									X			
Ott 2016	X	X									X			
Raju 2016	X							X						
Rodríguez 2016											X			
Savelski 2017											X			
Hindiyeh 2018						X								
Hänsel 2019	X								X		X	X	X	X
Jeswani 2019									X		X	X	X	X
Li 2019														X
Parvatker 2019	X	X									X			
Renteria 2019	X		X											
Renteria 2019							X							
Grimaldi 2020	X	X									X			
Sharma 2020						X								
Siegert 2020													X	X
Siegert 2020	X	X				X		X			X	X	X	X
Zhu 2020	X	X									X			
Fulford 2021	X						X				X	X	X	X
Kong 2021	X	X									X			
Wang 2021						X					X			
Yang 2021	X	X									X			
Bassani 2022	X							X						
Budzinski 2022	X		X								X			
Mohan 2022	X	X									X			
Schulte 2022													X	X
Sharma 2022	X	X									X			

Appendix 3

List of IPCC GWP 100a results values of the LCAs assessed

Name	Family	Scope	Value	unit	Functional unit	Harmonized categories FU	Reference
Dexmedetomidine	Chemical	Cradle to gate	3006	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Morphine	Chemical	Cradle to gate	1506	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Hydromorphone	Chemical	Cradle to gate	799	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Midazolam	Chemical	Cradle to gate	444	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Phenylephrine hydrochloride	Chemical	Cradle to gate	171	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Rocuronium Bromide	Chemical	Cradle to gate	144	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Ketamine	Chemical	Cradle to gate	140	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Remifentanil	Chemical	Cradle to gate	103	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Fentanyl	Chemical	Cradle to gate	96	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Ephedrine Hydrochloride	Chemical	Cradle to gate	82	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Glycopyrrolate	Chemical	Cradle to gate	76	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Ondansetron	Chemical	Cradle to gate	37	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Ropivacaine HCl	Chemical	Cradle to gate	36	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Epinephrine	Chemical	Cradle to gate	34	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Lidocaine	Chemical	Cradle to gate	29	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Bupivacaine HCl	Chemical	Cradle to gate	23	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Neostigmine methylsulfate	Chemical	Cradle to gate	22	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Propofol	Chemical	Cradle to gate	21	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Sugammadex	Chemical	Cradle to gate	12	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)

Succinyl choline	Chemical	Cradle to gate	11	kgCO2-eq / kg	None	None	(Parvatker et al., 2019)
Morphine	Chemical	Cradle to gate	2040	kgCO2-eq / kg	production of 100 mg in 100 mL of intravenous morphine	Product oriented	(McAlister et al., 2016)
Z-isomeric	Chemical	Cradle to gate	2250	kgCO2-eq / kg	None	None	(Ott et al., 2014)
Penicillin V	Chemical	Cradle to gate	6,02	kgCO2-eq / kg	None	None	(Brunet et al., 2014)
4-D-Erythronolactone (Batch process)	Chemical	Cradle to gate	14	kgCO2-eq / kg	to produce a reaction mixture containing 49.6 kg of 4-DEL within 5 days	Batch oriented	(Lee et al., 2016)
4-D-Erythronolactone (Conituous process)	Chemical	Cradle to gate	21	kgCO2-eq / kg	to produce a reaction mixture containing 49.6 kg of 4-DEL within 5 days	Batch oriented	(Lee et al., 2016)
sitaglipti n	Chemical	Cradle to gate	547,76	kgCO2-eq / kg	producing 1 kg of sitagliptin monophosphate	API oriented	(Zhu et al., 2020)
Eudorlin (Ibuprofen)	Chemical	Cradle to grave	36,25	kgCO2-eq / kg	treatment of an adult in Germany with the purpose of pain relief for 4 days	Function oriented	(M.-W. Siegert et al., 2020)
7-ACA - Chemical route	Chemical	Cradle to gate	387	kgCO2-eq / kg	A massbased functional unit of 1 kg of 7-ACA was chosen as the basis for the comparison	API oriented	(Henderson et al., 2008)
7-ACA - Enzymatic route	Chemical	Cradle to gate	205	kgCO2-eq / kg	A massbased functional unit of 1 kg of 7-ACA was chosen	API oriented	(Henderson et al., 2008)

					as the basis for the comparison		
Chemical	Chemical	Cradle to gate	67,6	kgCO2-eq / kg	1 kg of API	API oriented	(Wernet et al., 2010)
Tablet	Chemical	Cradle to gate	7,71	kgCO2-eq / tablet	None	None	(Hindiyeh et al., 2018)
Tablet	Chemical	Cradle to gate	2,06	kgCO2-eq / tablet	None	None	(Hindiyeh et al., 2018)
Improvac	Conjugated protein	Cradle to gate	- 1 kg of pig live weight : 6,70 - 1 kg of pig carcass after dressing : 8,75 - 1 kg of lean meat : 15,82	kgCO2-eq / FU	- 1 kg of pig live weight - 1 kg of pig carcass after dressing - 1 kg of lean meat	Function oriented	(Pfizer, 2012)
Inhaler - pMDI (Berodual®)	Device	Cradle to grave	16,484	kgCO2-eq / unit	None	None	(Hänsel et al., 2019)
Inhaler - pMDI (Atrovent®)	Device	Cradle to grave	14,585	kgCO2-eq / unit	None	None	(Hänsel et al., 2019)
Inhaler - Respimat® (Berodual®)	Device	Cradle to grave	0,784	kgCO2-eq / unit	None	None	(Hänsel et al., 2019)
Inhaler - Respimat® (Spiriva®)	Device	Cradle to grave	0,775	kgCO2-eq / unit	None	None	(Hänsel et al., 2019)
HFC-134a pMDI	Device	Cradle to grave	0,263	kgCO2-eq / dose	delivery of 1 dose of inhaled medicine'.	Patient oriented	(Jeswani and Azapagic, 2019)
HFC-227ea pMDI	Device	Cradle to grave	0,697	kgCO2-eq / dose	delivery of 1 dose of inhaled medicine'.	Patient oriented	(Jeswani and Azapagic, 2019)
HFC-152a pMDI	Device	Cradle to grave	0,02	kgCO2-eq / dose	delivery of 1 dose of inhaled medicine'.	Patient oriented	(Jeswani and Azapagic, 2019)

DPI	Device	Cradle to grave	0,009	kgCO2-eq / dose	delivery of 1 dose of inhaled medicine'.	Patient oriented	(Jeswani and Azapagic, 2019)
Enzyme, PGYL petroleum based glycerin	Enzyme	Cradle to gate	25	kgCO2-eq / kg	None	None	(Kim et al., 2009)
Enzyme, BGYL_M biobased glycerin	Enzyme	Cradle to gate	23	kgCO2-eq / kg	None	None	(Kim et al., 2009)
Enzyme, BGYL_S biobased glycerin	Enzyme	Cradle to gate	16	kgCO2-eq / kg	None	None	(Kim et al., 2009)
Bacterial alphaamylase	Enzyme	Cradle to gate	1	kgCO2-eq / kg	None	None	(Nielsen et al., 2007)
Fungal glucoamylase	Enzyme	Cradle to gate	6,8	kgCO2-eq / kg	None	None	(Nielsen et al., 2007)
Fungal phytase	Enzyme	Cradle to gate	2	kgCO2-eq / kg	None	None	(Nielsen et al., 2007)
Bacterial protease	Enzyme	Cradle to gate	4,1	kgCO2-eq / kg	None	None	(Nielsen et al., 2007)
Bacterial protease	Enzyme	Cradle to gate	10,1	kgCO2-eq / kg	None	None	(Nielsen et al., 2007)
mAb	Monoclonal antibody	Cradle to gate	31000	kgCO2-eq / kg	the set of operations required to Fill and Finish (F&F) a 20 ml vial, stoppered and capered which contains 608.8 mg of freeze dried infliximab powder (including excipients).	Product oriented	(Renteria Gamiz et al., 2019a)
mAb	Monoclonal antibody	Cradle to gate	22700	kgCO2-eq / kg	None	None	(Budzinski et al., 2022)

mAb	Monoclonal antibody	Cradle to gate	20000	kgCO2-eq / kg	2.5 ml of the Pre-Formulated Bulk (PFB) – the drug substance formulated to the desired final composition – containing 100 mg of API which is equivalent to the required API content per unit dose (vial).	Product oriented	(Renteria Gamiz et al., 2019a)
mAb	Monoclonal antibody	Cradle to gate	276600	kgCO2-eq / kg	a provision of the annual mAb demand to the Japanese market		(Amasawa et al., 2021)
mAb	Monoclonal antibody	Cradle to gate	137235	kgCO2-eq / kg	a provision of the annual mAb demand to the Japanese market		(Amasawa et al., 2021)
Polymer vials system	Packaging	Cradle to grave	5,05E-02	kgCO2-eq / unit	The functional unit used for further calculation consists of a thousand vials.	Batch oriented	(Belboom et al., 2011)

Glass vials system	Packaging	Cradle to grave	6,56E-02	kgCO2-eq / unit	The functional unit used for further calculation consists of a thousand vials.	Batch oriented	(Belboom et al., 2011)
Blister Alu-alu	Packaging	Cradle to grave	409,6	kgCO2-eq / FU	The functional unit is taken as material required for packing 1 lakh (1,00,000), 500mg of paracetamol tablets.	Batch oriented	(Raju et al., 2016)
Blister packing	Packaging	Cradle to grave	102,4	kgCO2-eq / FU	The functional unit is taken as material required for packing 1 lakh (1,00,000), 500mg of paracetamol tablets.	Batch oriented	(Raju et al., 2016)
Paracetamol - tablet	Process		6,09	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		2,78	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		2,78	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’	Batch oriented	(Sharma et al., 2020)

					paracetamol tablets.		
Paracetamol - tablet	Process		7,21	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		5,1	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		3,31	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		2,42	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,23	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,322	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)

Paracetamol - tablet	Process		1,23	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,23	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,023	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,67	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		5,47	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,37	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,37	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’	Batch oriented	(Sharma et al., 2020)

					paracetamol tablets.		
Paracetamol - tablet	Process		7,09	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		4,38	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,65	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		1,2	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,61	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,161	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)

Paracetamol - tablet	Process		0,61	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,61	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,0118	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Paracetamol - tablet	Process		0,824	kgCO2-eq / FU	the API required to produce ‘one hundred thousand’ paracetamol tablets.	Batch oriented	(Sharma et al., 2020)
Freeze drying process	Process	Gate to gate	0,098	kgCO2-eq / vial	2.5 ml of the Pre-Formulated Bulk (PFB) – the drug substance formulated to the desired final composition – containing 100 mg of API which is equivalent to the required API content per unit dose (vial).	Product oriented	(Renteria Gamiz et al., 2019b)

Homogeneous system	Waste	End of life	0,144	kgCO2-eq / FU	the functional unit for both processes was fixed as environmental impacts in removing 1 g of COD per litre of treated wastewater.	Function oriented	(Rodríguez et al., 2016)
Heterogeneous system	Waste	End of life	0,025	kgCO2-eq / FU	the functional unit for both processes was fixed as environmental impacts in removing 1 g of COD per litre of treated wastewater.	Function oriented	(Rodríguez et al., 2016)

Appendix 4

List of stakeholders identified with the related harmonized family

Stakeholder	Family	Harmonized family	Geel framework	Country	Reference
	academic clinicians	Research	Research network	Europe	Saesen
	patient organization	Patients & the Public	Societal groups	Europe	Saesen
	regulators	Public authorities	Public authorities	Europe	Saesen
	health technology assessment agency	Purchasers & Payers	Financial network	Europe	Saesen
	payer	Purchasers & Payers	Financial network	Europe	Saesen
	pharmaceutical industry	Pharmaceutical industry	Producer network	Europe	Saesen
Individual member of the public	IPCO+	Patients & the Public	Societal groups	Europe	Hines
Patient or consumer organisation	IPCO+	Patients & the Public	Societal groups	Europe	Hines
Advocacy group	IPCO+	Patients & the Public	Societal groups	Europe	Hines
Health care professional organisation	HCP	Health care professional	User groups	Europe	Hines
Health care professional	HCP	Health care professional	User groups	Europe	Hines
Veterinarian	HCP	Health care professional	User groups	Europe	Hines
Academic researcher	Research	Research	Research network	Europe	Hines
Learned society	Research	Research	Research network	Europe	Hines
European research infrastructure	Research	Research	Research network	Europe	Hines
Other scientific organisation	Research	Research	Research network	Europe	Hines
EU Regulatory partner / EU Institution	Public body	Public authorities	Public authorities	Europe	Hines
Health technology assessment body	Public body	Public authorities	Public authorities	Europe	Hines
Payer	Public body	Public authorities	Public authorities	Europe	Hines
Pharmaceutical industry (individual company, SME, trade association)	Public body	Public authorities	Public authorities	Europe	Hines
Ministère des solidarités et de la santé	Public health actors	Public authorities	Public authorities	France	AVISE

CNS	Public health actors	Public authorities	Public authorities	France	AVISE
HCSP	Public health actors	Public authorities	Public authorities	France	AVISE
HAS	Public health actors	Public authorities	Public authorities	France	AVISE
Santé publique France	Health agency	Public authorities	Public authorities	France	AVISE
IRDES	Research institutes	Research	Research network	France	AVISE
INSERM	Research institutes	Research	Research network	France	AVISE
INC	Research institutes	Research	Research network	France	AVISE
Choum	Resource centers and observatories	Societal groups	Societal groups	France	AVISE
FNORS	Resource centers and observatories	Societal groups	Societal groups	France	AVISE
PAPS	Resource centers and observatories	Societal groups	Societal groups	France	AVISE
C@rto Santé	Resource centers and observatories	Societal groups	Societal groups	France	AVISE
Mutualité Française	Health mutuals	Purchasers & Payers	Financial network	France	AVISE
ADMR	Health, Social, medico-social organizations	Societal groups	Societal groups	France	AVISE
FEHAP	Health, Social, medico-social organizations	Societal groups	Societal groups	France	AVISE
FNCS	Health, Social, medico-social organizations	Societal groups	Societal groups	France	AVISE
UNA	Health, Social, medico-social organizations	Societal groups	Societal groups	France	AVISE
UNIOPSS	Health, Social, medico-social organizations	Societal groups	Societal groups	France	AVISE
ARS	Public establishments	Public authorities	Public authorities	France	AVISE
Assurance maladie	Public establishments	Public authorities	Public authorities	France	AVISE
Banque des territoires	Public establishments	Public authorities	Public authorities	France	AVISE
CFF	Fondations	Societal groups	Societal groups	France	AVISE
Fondation Crédit agricole	Fondations	Societal groups	Societal groups	France	AVISE
Fondation de France	Fondations	Societal groups	Societal groups	France	AVISE
MACIF fondation	Fondations	Societal groups	Societal groups	France	AVISE

Fondation Médéric Alzheimer	Fondations	Societal groups	Societal groups	France	AVISE
BPI France	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
CCA	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
France eHealth tech	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
Autonom'lab	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
Bond'innov	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
Lecentsept	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
ICM	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
La paillasse	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
Prevent 2care lab	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
Forum LLSA	Specialst of health support actors	Societal groups	Societal groups	France	AVISE
CNAV	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
CARSAT	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
CNSA	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
MSA	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
Agircetarrco	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
AG2R la mondiale	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
Malakoff médéric	Solidarity funds and social security organizations	Societal groups	Societal groups	France	AVISE
	Policy makers & Politicians	Public authorities	Public authorities	Australia	Ryan
	Policy makers & Politicians	Public authorities	Public authorities	Australia	Ryan
	Policy makers & Politicians	Public authorities	Public authorities	Australia	Ryan
	Policy makers & Politicians	Public authorities	Public authorities	Australia	Ryan
	Policy makers & Politicians	Public authorities	Public authorities	Australia	Ryan

	Policy makers & Politicians	Public authorities	Public authorities	Australia	Ryan
	Purchasers & Payers	Purchasers & Payers	Financial network	Australia	Ryan
	Purchasers & Payers	Purchasers & Payers	Financial network	Australia	Ryan
	Purchasers & Payers	Purchasers & Payers	Financial network	Australia	Ryan
	Purchasers & Payers	Purchasers & Payers	Financial network	Australia	Ryan
	Purchasers & Payers	Purchasers & Payers	Financial network	Australia	Ryan
	Purchasers & Payers	Purchasers & Payers	Financial network	Australia	Ryan
	Principal Investigators	Research	Research network	Australia	Ryan
	Principal Investigators	Research	Research network	Australia	Ryan
	Principal Investigators	Research	Research network	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Health Care Providers	Health care professional	User groups	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Product Makers	Pharmaceutical industry	Producer network	Australia	Ryan
	Patients & the Public	Patients & the Public	Societal groups	Australia	Ryan

	Patients & the Public	Patients & the Public	Societal groups	Australia	Ryan
	Patients & the Public	Patients & the Public	Societal groups	Australia	Ryan
	Patients & the Public	Patients & the Public	Societal groups	Australia	Ryan
Consumers	Consumers	Patients & the Public	User groups	US	Niles
Employers	Employers	Patients & the Public	User groups	US	Niles
Hospitals	Hospitals	Health care professional	User groups	US	Niles
Nursing and residential care facilities	Nursing and residential care facilities	Health care professional	User groups	US	Niles
Physicians and other healthcare practitioners	Physicians and other healthcare practitioners	Health care professional	User groups	US	Niles
Home healthcare services	Home healthcare services	Health care professional	User groups	US	Niles
Outpatient care centers and ambulatory healthcare services	Outpatient care centers and ambulatory healthcare services	Health care professional	User groups	US	Niles
Laboratories	Laboratories	Health care professional	User groups	US	Niles
Government	Government	Public authorities	Public authorities	US	Niles
Insurance companies	Insurance companies	Purchasers & Payers	Financial network	US	Niles
Educational and training organisations	Educational and training organisations	Societal groups	Societal groups	US	Niles
Research organizations	Research organizations	Research	Research network	US	Niles
Professional associations	Professional associations	Societal groups	Societal groups	US	Niles
Pharmaceutical companies	Pharmaceutical companies	Pharmaceutical industry	Producer network	US	Niles
Central government	Central government	Public authorities	Public authorities	China	Shao
Provincial governments	Provincial governments	Public authorities	Public authorities	China	Shao
local governments	local governments	Public authorities	Public authorities	China	Shao
Medical institutions	Medical institutions	Health care professional	User groups	China	Shao
Pharmaceutical manufacturers	Pharmaceutical manufacturers	Pharmaceutical industry	Producer network	China	Shao
Delivery enterprises	Delivery enterprises	Supplier	Suppliers	China	Shao
Patients	Patients	Patients & the Public	User groups	China	Shao
Medical insurance institutions	Medical insurance institutions	Purchasers & Payers	Financial network	China	Shao

Mass media	Mass media	Societal groups	Societal groups	China	Shao
Community	Community	Societal groups	Societal groups	China	Shao
the Drug stores	the Drug stores	Health care professional	User groups	China	Shao
Members of the public	Members of the public	Patients & the Public	User groups	Africa	Kamau
Patients	Patients	Patients & the Public	User groups	Africa	Kamau
Patients' family, friends	Patients' family, friends	Patients & the Public	User groups	Africa	Kamau
Clinicians, counselors	Clinicians, counselors	Health care professional	User groups	Africa	Kamau
Care providers	Care providers	Health care professional	User groups	Africa	Kamau
Researchers	Researchers	Research	Research network	Africa	Kamau
Healthcare facilities	Healthcare facilities	Health care professional	User groups	Africa	Kamau
Biomedical service providers	Biomedical service providers	Health care professional	User groups	Africa	Kamau
Health insurers	Health insurers	Purchasers & Payers	Financial network	Africa	Kamau
Communities	Communities	Patients & the Public	User groups	Africa	Kamau
Population groups	Population groups	Societal groups	Societal groups	Africa	Kamau
Educators	Educators	Societal groups	Societal groups	Africa	Kamau
Funders (African/International)	Funders (African/International)	Purchasers & Payers	Financial network	Africa	Kamau
Global policy makers	Global policy makers	Public authorities	Public authorities	Africa	Kamau
Regional policy makers	Regional policy makers	Public authorities	Public authorities	Africa	Kamau
National policy makers	National policy makers	Public authorities	Public authorities	Africa	Kamau

Appendix 5

2021 benchmark of the eco-design strategies of 20 pharmaceutical companies

Benchmark	Targets		Actions known or claimed	
	Ecodesign	Packaging	Ecodesign	Packaging
Abbvie	- No specific goals	- No specific goals	-	-
Allergan	- No clear ecodesign targets			
Amgen	2027 target design: "Amgen has created a portfolio of projects and initiatives to achieve the targeted reductions by 2027. We track the results of these projects and initiatives as progress towards the reduction targets, counting results where reduction is confirmed through a formal measurement and verification process. We believe that this approach provides more thoughtful and transparent progress towards our targets."	-	-	-
Astrazeneca	- By 2025: 90% of API syntheses meet resource efficiency target at launch	- No official target & No KPI	- Tool for solvent selection (available with ACS GCIPR) -LCAs performed	-
BI	- No official target & No KPI	- No official target & No KPI	- LCAs performed -Claim to use iGaL metric (Green Chemistry)	- Ecodesign tool developed (by Quantis but not mentioned on the website of BI)
Biogen	- No clear ecodesign targets		- Claims to have a life cycle approach	
BMS	- Mainly green chemistry, not ecodesign By 2020 >90% of new products in R&D portfolio, and packaging of prioritized products, assessed for improved environmental impact	- No specific goals	-	-
GSK	-By 2030 25% environmental impact reduction for product and packaging throughout its whole life cycle	- By 2021 Remove PVC in all secondary packaging . By 2025 Health Care 100% product packaging recyclable/reusable where quality and safety permits (Ellen McArthur membership) -By 2030 Eliminating single use plastics in our operations (excluding plastics critical to RD , HS , and regulatory obligations)	- FLASC tool (since 2002) -2009 : 500 FLASC assessments -LCAs performed	- WRAP tool (since 2002)
Gilead	- No clear ecodesign targets but claims to work on steps of life cycle (except EoL and use)		- claims to work on steps of life cycle (except EoL and use)	

Benchmark	Targets		Actions known or claimed	
	Ecodesign	Packaging	Ecodesign	Packaging
J&J	- New and existing products representing 20% of Johnson & Johnson revenue achieve EARTHWARDS recognition for sustainable innovation improvements -Claim to have Eco-design process for consumer product	- Increase the recyclability of our Consumer product packaging to 90+% (on a weight basis) via design and partnerships in five key markets where mature recycling infrastructure exists (Canada, France, Germany, UK and U.S.)	- Claim to perform LCA	-
Lilly	No specific goals	- No specific goals	-	-
Merck & co	No specific goals (integrate sustainability by 2030)	- No specific goals	-	-
Novartis	No official target & No KPI	- 2025 : Elimination of PVC in packaging (except primary) and reduce waste disposal by half versus 2016 levels 2030: Be plastic neutral with all new products meeting sustainable design principles.	- LCA Breezhaler (focus CO2)	- Workshop with ADELPHE on-going (ie : primary packaging blister PVC/alu)
Novo nordisk		-	- Claims to work on devices recovery / recycling (pilot take back scheme in 2020) -Have performed LCA	-
Pfizer	- No specific goals	- No specific goals	- LCAs performed	-
Roche	- By 2020: Score 10 products -By 2030: Products (Improve Product Stewardship score) - 50%	- No official target & No KPI	-	-
Sanofi	- By 2025 Eco-design for 100% of new products -By 2030 100% of top-20-selling products	- By 2030 Eco-packaging for 100% of products.	- LCAs performed -Workshop for devices	- In 2016: French award : « Oscar de l'emballage » -Workshop with ADELPHE on-going (ie : blister)
Takeda	- No clear ecodesign targets		- Claims to apply circular economy principles Claims to consider product in a life cycle perspective	
Bayer	- No clear ecodesign targets		- No approach in a life cycle perspective	
Teva	- No clear ecodesign targets			

Appendix 6
Semi-structured interview
Product portfolio:

- What is the range of products that the division / business unit / department develops / manage? Main API technology, association galenic forms/packaging.
    - API: Which technologies are used (proposition based on literature: synthetic organic chemicals, cell culture, egg-based cultivation, conjugate vaccines, plant-base extraction, animal and human derived)? What are criteria used to differentiate between API (technologies, effect, formulation)?
    - Which galenic forms are associated with which format/type of packaging?
        - Galenic forms: liquids (liquids, teas, pressurised aerosols), semi-liquids (gels and sols, ointments, creams), Injections(ampoule, pre-filled syringe, vials, cartridges & pens, infusions) , solid (powders & granulates, tablets, coated tablets, capsules)
        - Packaging: Liquids (aerosols, bulbs/ampoule, bottle packs, soft capsules, bottles, pouch, capsules, pouch), injections (pouch, bottle syringe, cartridge & pens, bulbs, capsule/ampoule, bottle, vials), solid (blister, strip, pillbox, box, roller, bottle, sachet), semi-solids (tube, blister, jar)

Repartition of the portfolio:

- In your everyday projects, how many of them do you consider as evolutions of existing product ranges?
    - With minor changes: renew the product range packaging, new delivery mode?
    - With major changes (e.g. new distribution markets ?)
- How would you define an innovative projects? A new API/galenic form, a new production path for an API/galenic form?

New product:

- What are the circumstances which lead to a new market authorisation? Is this always associated to a new product design?
- For the following case, do you consider that a product is redesigned?
    - Industrialisation of new API/Galenic form/Packaging on a new production line
    - Change of ingredients, raw materials (for cost, safety, supply reasons)?
    - Change of product delivery mode / packaging ?
    - New test requirements for market authorisation?

Synthesis:

- With all those questions in mind, do you have a different development cycles depending on the type of design changes for you product?

Key competencies in a design team

- What are the key competencies or trade needed when putting together a design team at each specific moment (early design / R&D / Innovation)?

    - What are their day to day activities? Bench work? Simulation? Interaction with suppliers....
- In those core competencies / trade, do you know if other Sanofi branch rely on them?

Trade common to Sanofi business model

- In the core design team, is there a trade/craft that is also present in other units of Sanofi or that is mutualized across several units?
    - For example, do you have your own packaging experts or do you rely on Sanofi packaging team?
    - For test and simulation, do you sometimes use Sanofi shared facilities and staff? How to exchange information with them (format of test results)?..

Use of trade outside of the unit

- When and how do you interact with Sanofi stakeholders outside of your core team?
    - Ex: when do you start working with packaging designers? When you interact with decision makers, how to you facilitate your exchanges?
- Are there moments in the design process when you rely on external stakeholders to support the process? External stakeholders can be outside your unit or outside Sanofi.

Indicators followed form start to finish

- What are the KPIs to follow throughout the project?
    - Are they modified depending on the project stage?

Gate dependent indicators:

- What indicators are used to inform the decision to continue the process at a gate review?

Design specific indicators:

- Do you have indicators used at a specific design stage?
- What are the KPIs that are documented at the end of the design process (to be used for next projects, such as experience feedback)?

Format:

- Do you have a document / a tool that consolidates all those indicators and that follows the project through the design gates?

Consolidation KPIs

- What type of data do you use to consolidate the KPIs mentionned above?
- Do you account for uncertainty of data in early stage of product development?
- Do you rely on KPPI, and if yes at which stage and how? Who is responsible for integrating KPPIs data into the product design process?

Key moments for environmental data (when 1st define – by who; when modify - by who; when last modify - by who) – always ask if the information is documented in a digital format

- Raw materials:
    - At the beginning of the process, do you pre-identify raw materials candidates and processing/synthesis routes?

    - When do you start the discussion with suppliers / manufacturing facilities?
    - Do you audit the suppliers / manufacturing facilities when transitioning from bench development to industrialization? On what aspects?
    - What and how are raw materials tested?
- Formulation:
    - What are in the handover documents from API development to API/Galenic form formulation?
    - If adjustment are needed on the API when formulating the product, how is the information feed back to the API development team
    - When and how is the formulation tested?
    - When is the manufacturing facilities definitely fixed?
- Packaging / Transport / Storing:
    - How do you transmit the storing constrains for the API/Galenic form to the packaging expert?
    - When and how is the product /packaging tested?
- Usage
    - When do you define the use case (dosage, galenic form...)?
- End of Life
    - When do you test for toxicity and what is the format for documentation?

Updating data

- When do you review the data already input to define KPIs to check if there is no deviation?

Appendix 7

Example of the calculation of the second experimentation, with a focus on Global warming indicator.

1. A score was set regarding the life cycle steps of a medicine (API, formulation, packaging, distribution, end of life) for each deliverable of each phase (research, early development, late development, market) of the NPD process.

   Non exhaustive examples of deliverables and related potential environmental scoring

Phase	Deliverable	S_{API}	$S_{Formulation}$	$S_{Packaging}$	$S_{Distribution}$	$S_{End\ of\ life}$
Early development	Define strategy for proposed starting materials.	4	4	2	1	1
Early development	Confirm suppliers selection	3	3	3	3	3
Late development	Define Drug product - Commercial formulation & process Define Drug product - Commercial primary container	3	3	4	3	2

2. With the formula below, a breakdown was then calculated

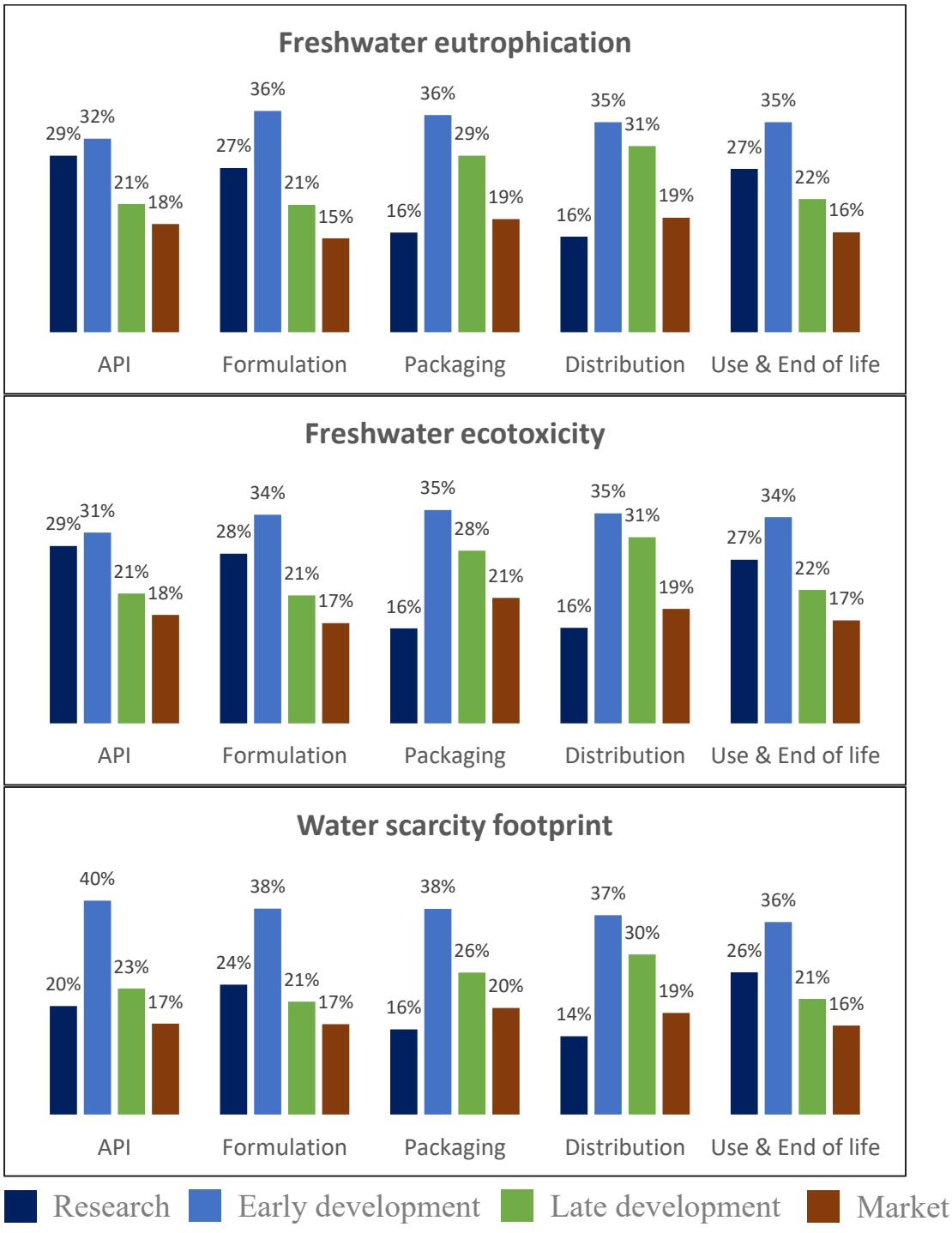
   For the Life Cycle step S_{API}: $\%_{Phase\ a} = {\sum S_{API\ of\ phase\ a}}/{\sum S_{API}}$

In this example:

- For the Life Cycle step S_{API}: $\%_{\text{Early development}}$ = (4+3) / (4+3+3) = 70 %
- For the Life Cycle step S_{API}: $\%_{\text{Late development}}$ = (3) / (4+3+3) = 30 %

Appendix 8

Breakdown by lifecycle stage of the level of influence of the deliverables of the medicine NPD, for the freshwater eutrophication, freshwater ecotoxicity and water scarcity footprint per Lifecycle steps (API, formulation, packaging, distribution and use & end of life), based on 263 deliverables assessed



Appendix 9

Unstructured interview, list of topics raised

- Role & function within the pharmaceutical company of the interviewee
- Pharmaceutical R&D objectives
- Current trends regarding biotechnology and chemistry
- Transformation of sites from Chemistry to Biotechnology
- Industrialization: from R&D lab scale to mass production
- R&D strategies
- R&D organization
- R&D functions
- R&D stakeholders
- Project governance
- R&D process & iterations
- Potential structure for an Eco-design maturity model for the pharmaceutical R&D
- Potential applicability / use of an Eco-design maturity model for the pharmaceutical R&D

Appendix 10

unstructured interview, profile of the interviewee

Affiliation	Background	Environmental knowledge	Country	Scope of missions
Pharmaceutical industry	• 20 years in pharma R&D in diverse phases • Pharmacist	Conducted a project of Circular Economy in pharma R&D	France	International

Appendix 11
survey, list of questions

Introduction

1. What is your job title?
2. For which R&D function are you working for?
3. What is your role within this function?
4. How many scientific R&D projects are you and have you been working on?
5. For how long have you been working in R&D?
6. Are you familiar with the global R&D value chain? (e.g. : Research, Pre-clinical trials, phase 1, etc.)

Eco-design of new medicine

7. What means Eco-design for you?
8. In your opinion, Eco-design is: Important / The future / A better way to develop drugs / complicating the process / Something you would like to know more about
9. Based on your experience, do you think that Eco-design is currently implemented within your project(s)? - If "Yes", why? / If "No", what prevent you from doing it?
10. What are the constraints that you might face regarding the integration of Eco-design

Eco-design Implementation

11. What do you perceive to be the biggest hurdle to implementing Eco-design in the R&D processes?
12. In your experience, which choices during the project phases have impacts on the environmental profile of the final product?

13. *The Eco-design maturity represents the level of a specific project regarding the integration of eco-design practices within its processes, such as the use of all the Eco-design tools available.*

    How would you like to be kept up to date regarding the evolution of the Eco-design maturity of your project?
14. In your opinion, which governance committees should integrate Eco-design informations?
15. If "Strategic Sourcing Committee" is selected, please specify the committee you are thinking about.

Further comments

16. Do you have any additional comments?
17. If you would be willing to talk with us more about this topic, please leave your contact details in the box below.

Appendix 12:
User tests, list of profiles

User number	Background	Environmental knowledge	Country	Scope of missions
User 1	• 19 years in pharma R&D in diverse phases • PhD chemistry	None	Germany	International
User 2	• 22 years in pharma R&D in diverse phases • Pharmacist	None	France	International
User 3	• 2 years in R&D • PhD immunology	None	Germany	International
User 4	• 20 years in pharma R&D in diverse phases	None	France	International
User 5	• 18 years in pharma R&D in diverse phases • PhD Organic chemistry	None	France	International
User 6	• 10 years in pharma R&D in diverse phases	None	China	International
User 7	• 11 years in pharma R&D in diverse phases •	None	France	International

Appendix 13:
User tests, list of statements to assess

S1. Overall, I am satisfied with how easy it is to use this system.
S2. It is simple to use this system.
S3. I can effectively complete my work using this system.
S4. I am able to complete my work quickly using this system.
S5. I am able to efficiently complete my work using this system.
S6. I feel comfortable using this system.
S7. It was easy to learn to use this system.
S8. I believe I became productive quickly using this system.
S9. Whenever I make a mistake using the system, I recover easily and quickly.
S10. The information (on-screen messages, documentation) provided with the system is clear.

S11. It is easy to find the information I need.
S12. The information provided with the system is easy to understand.
S13. The organization of information in the system is clear.
S14. The interface of the system is pleasant.
S15. I like using the interface of this system.
S16. This system has all the functions and capabilities I expect it to have.
S17. Overall, I am satisfied with this system.

Appendix 14:

First prototype, meso level – list of practices

Leadership & Tactical Integration

- Integration
  1. The integration of Eco-design is analyzed and followed-up with the Eco-design management tools in place.
  2. The dimensions of Eco-design are fully integrated into all planning perspectives. Eco-design indicators are fulfilled and followed-up during the R&D phase / project.
  3. Results of the Eco-design tools are provided all along the drug development process and allow the optimization of the environmental performance of the product.
  4. Eco-design practices and tools are systematically incorporated into the development of products and processes.
  5. Product environmental footprint goals are deployed among employees of different levels at the project / function.
  6. The environmental performance of the product/process is checked during the identified governance committees in a systemic manner.
- Monitoring & Control
  7. Eco-design related data are considered at the same level as the benefit-risk balance.
  8. Eco-design aspects and environmental goals are part of the product target specification.
  9. The collaborative network allowing the process of identifying Eco-design opportunities and risk is facilitated by a systemic process.
  10. Environmental aspects in the identification/qualification of potential suppliers are considered.

Eco-Design Training & Resources

- Training
  11. Awareness and understanding of the environmental issues throughout the life cycle of the product.
  12. The knowledge on the Eco-design approach and practices is disseminated.
  13. The improvement of Eco-design leadership, such as training, coaching programs, responsibility taking skills, etc., is encouraged by the managers (the stakeholders are trained about Eco-design).
- Resources
  14. Resources have been allocated for your project for Eco-design activities that were identified as necessary by your project team.
  15. Technologies allowing a better environmental performance are documented and made available to R&D stakeholders.
  16. Ensure commitment and support to conduct the activities related to Eco-design.
  17. The combined Eco-design tools are used contributing to the integration of environmental aspects into the New Product Development.

Collaboration & Communication

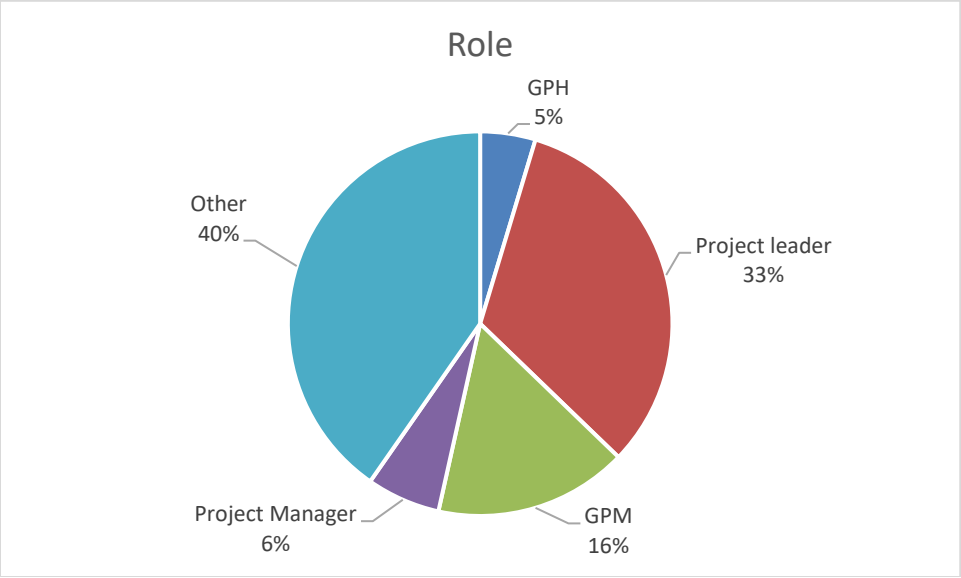
- Collaboration
  18. R&D stakeholders demonstrate environmental values leading Eco-design internal initiatives and directly engaging in collaborative networks.

19. R&D stakeholders consider the close relationship between several actors from different sectors and departments (multidisciplinary team) to be very important to manage projects.
20. Open, direct and collaborative communication among all members, without repressing initiatives, opinions, and ideas is promoted by the management.

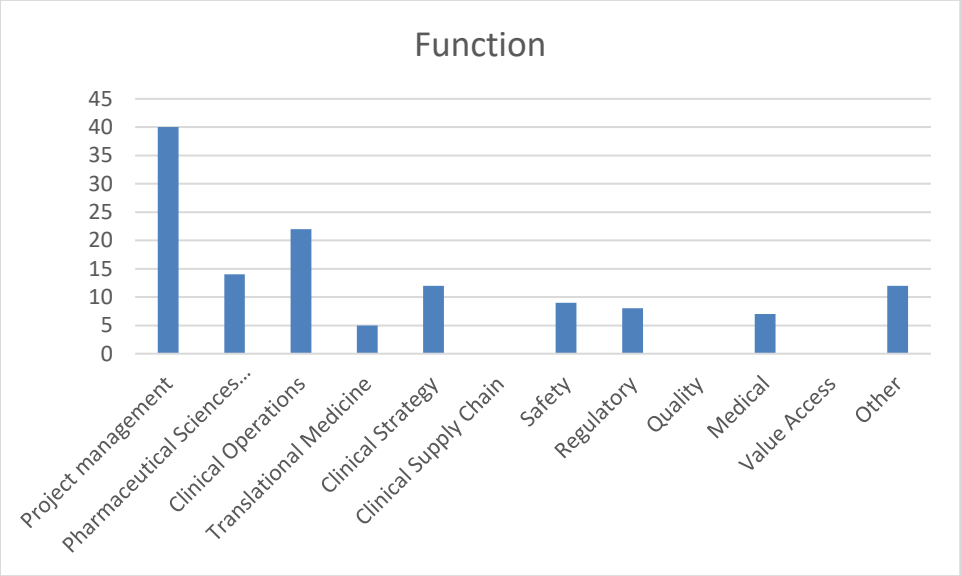
- Communication

21. Feedback from eco-design integration is shared within the company. A feedback system is used to evaluate and provide feedback to employees, particularly regarding environmental improvement efforts.
22. Various forms of dialogue and interaction with stakeholders guided by environmental aspects are promoted.

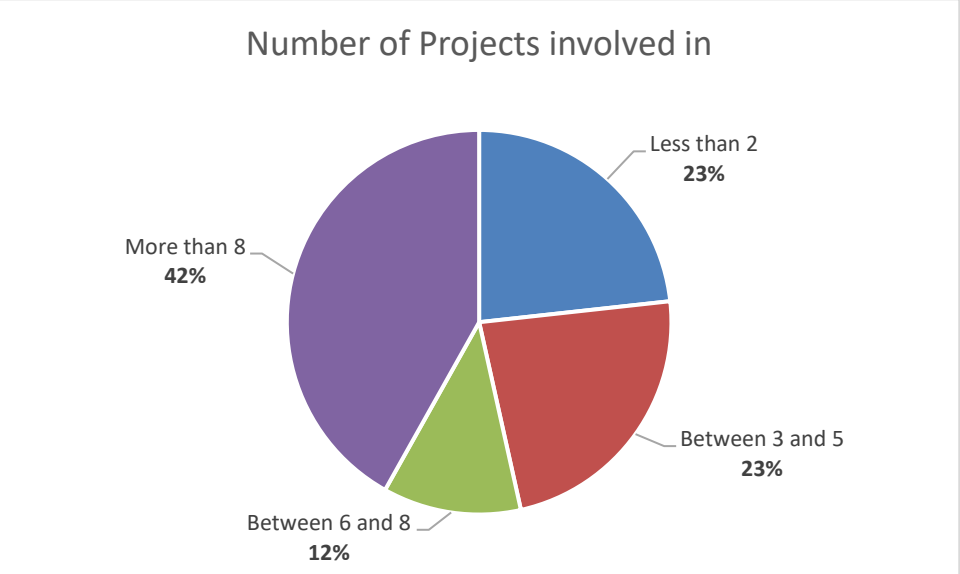
Appendix 15: survey, characteristics of respondents

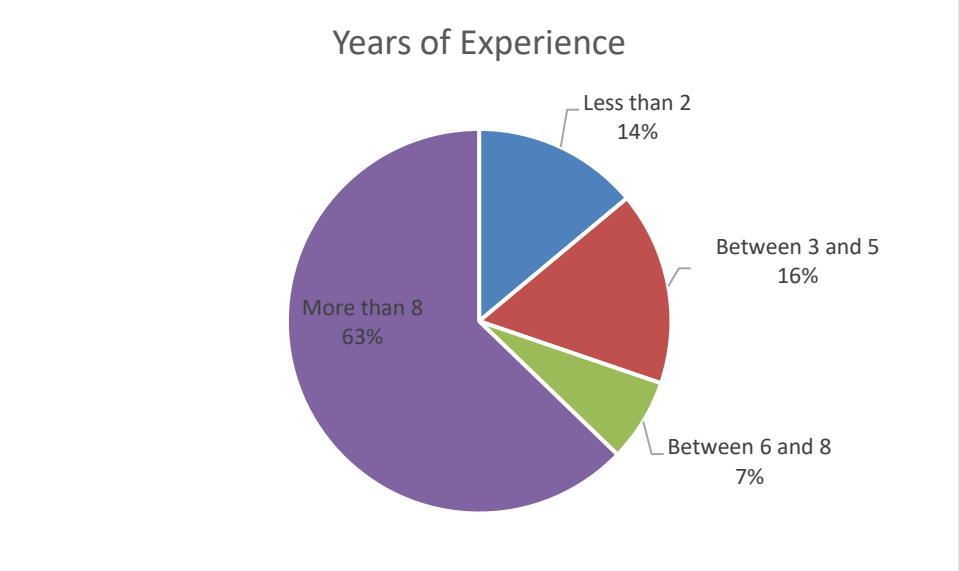


Role: Other	
TA Head Development	Study Medical Manager
Head GPPM	PPM
Manager of PMs	Pharmacovigilance Scientist
Global Development Project Management Head	CI analyst
Head of Device Regulatory	head of function
PM Head	OPCM
PDR	Drug Product Team Leader
Preclinical Safety Project Team Member	GSO
RA	GSM/PM
Global Medical Lead	Managing the collection of clinical data
GRA CMC China	US RA
Clinical Research Director	Risk Management Expert
planning manager	Global Regulatory Team Lead
risk management expert	Nonclinical Lead
Non clinical safety project representative	Pharmacokinetics Project Expert
Lead Clinical Research Director	Area Expert
Global Regulatory Team Lead	Leader of a team of Global Study Managers
Supporting function (Bioanalytical)	GSM
CRD	Study Medical Manager
Heath Value Translation Lead	Project leader for CRO Japan
TM lead	global study manager
Member of project team	cluster head
Demand & Supply Leader	Global Study manager
Project Team member	Team Head
CSO OPCM, Clinical Science Operation Operational Planning & Capactity Management	



Function: Other
PDR
Preclinical Safety
TO
PID&HVT
Global operations
TMED
Device Development
Research
Trial Operations
CSO trial operation
associate Global Study Manager
CMC project management





Appendix 16: survey, verbatim to the perceptions of which choices during the project phases have impacts on the environmental profile of the final product

different manufacturing milestones comes to mind, but also the way we select to conduct pre-clinical and clinical studies

Impact become bigger with project advancement

Design of the overall commercial model - sourcing, manufacturing, logistics, packaging, launch country selection
manufacturing process, choice of contractors (do they comply with eco-design aspects?)
CMC Manufacturing processes, Supply-Chain details (packaging, distribution, storage-conditions, etc.)
location of manufacturing
Primary container design and IMP components selection, including devices.
discovery: synthesis of new compounds; development: set up the manufacturing process
packaging design, device design, overly conservative with technical studies run
Manufacturing, destruction of assets
the chemical synthesis pathway; the manufacturing, analysis, packaging on different sites leading to shipment of the product
Every phase
API manufacturing process definition, definition of manufacturing lines cleaning processes, definition of secondary packaging (need for autoinjector), definition of box types, definition of shipment routes and distribution center locations,
packaging
Lab in research, lab in parallel to clinical development (bioanalysis, biomarkers...), choice of the dose, transition to industrialization, expedition of compound....
all CMC and manufacturing decisions. I.e. sites,...
clinical results
the competitive products environment
choice of manufacturing and location
CMC development, packaging, commercialization strategy etc.
- selection of formulation - route of administration - device selected
Starting materials and synthesis processes.
Device choices, chices of Sites to produce commercial products, production lines
the use of CMos in China whereas API/impurities could be manufactured locally in Europe or US.
transport
Design Input
CMC process, DS/DP manufacturing, IMP supply and destruction process
All.
integrated development from early stages, development tool choice
Synthesis of the molecule, manufacture of the product, primary container, other packaging materials
almost all but maisnly CMC, commercialization and distribution and clinical development,
The type of chemical entity e.g. small molecule, monoclonal antibody, etc, ...; How the drug is manufactured and where; Route of administration and the device used to administer it; Product packaging choices; Where we conduct our clinical trials (some countries manage carbon footprint more than others)
Choices about formulation, packaging and very importantly storage temperature,...
All steps, from selection of the intermediates for chemical design (or comparable steps for biologics) through packaging and marketing of approved compounds.
manufacturing
drug manufacturing

Packaging choices; storage conditions; manufacturing sites
mainly manufacturing processes
CMC process
Raw material and their sourcing. Composition and formulation, then metabolites that are rejected. Packaging and transport between different continents are also major impacts.
dosage form, manufacturing set up, manufacturing process (e.g., yield), distribution decisions, constraints on specifications
device / packaging choice
the global design at the IDP strategy design stage probably differences across the therapeutic areas
design of manufacturing process, choice of manufacturing locations and product distribution routes (supply chain).
Phase 2 and 3
all phases
Choice of CRO/vendor. But is should also be part of the discussion when a preferred provider is chosen. I don't know if this is a standard part of vendor selection, I was not involved in this.
Raw materials, single use technology, location of clinical trials, packaging,
All.
use of disposables
Choice as part of the risk management strategy to implement a digital tool to communicate key safety messages with patients and HCPs (instead of paper)
Raw materials, devices, manufacturing process, packaging….
Supply chain for the clinical and to be commercialized product Choice of the package Reducing wastage when defining dose and method of administration
- Supply chain - Selection of vendors/CROs for externalized activities
No comment as I need more understanding of Eco-Design..
Formulations and drug delivering systems, ...
way of administration and associated material used to product it, location of production, shipment of the drugs/investigational product
Reduce the number of data collected, chose vendors with multiple offices/warehouses worldwide to limit waste and shipments of samples. Design IMP containers that reduces waste.
Packaging.
packaging and manufacturing
At the time of final formulation preparation in P3。.
product discovery phase
Cell line, timelines, resources; degree of single-use material use
It needs to be considered right from the start of a program. Changing afterwards or during development cost much higher resources and efforts compared to make it eco-friendly from the beginning.
All steps involved in the life cycle of an asset have an impact on the profile.
NDA route selection Commercial packaging selection
I guess it's mainly for the drug substance synthesis process (at least for synthetics)
RM supplier/ DS/DP manufacturing/transport and up-to date facilities

starting material, synthesis process, suppliers and subcontractors selection and control
Earlier the phase, the better. Likely in discovery
CMC
All, but in crescendo from Ph 1 to registration
choice of participating countries, central versus local lab, decentralized CT

Appendix 17: survey, verbatim to the option "other" of the "constraints regarding Eco-design implementation"

Facing Constraints: Other
No information received at this point
Need to change our mindset to incorporate these considerations at all steps.
eco design is not a driver.
process actually in progress but not yet implemented
I just started at Sanofi
We have not yet defined the strategic goals.
Integrating the QR Code via the ePI company initiative a created new role and new processes for which there is not yet a GxP business System/Process owner which make difficult the E2E process consolidation
Decision not within my scope
Lack of capacity of packaging industry, induced Costs
some concrete exemples may help understand what we can do, think about...
budget
would like to understand the CO2 print foot.
more time might be required to develop new process vs projects timelines to be met
timelines are the most critical aspect and prohibit a lot of activities
at this stage of my project, integrating eco-design would mean allocate resources to it and increase project cost not the current trend...
I am not really sure what is possible.
See response to Q12

Appendix 18: Second prototype proposition, matrix levels of Eco-design maturity with the organizational and operational dimensions

Level	Organizational	Operational
1	• Eco-design practices are not applied or are applied in an incomplete way by the R&D functions • No clear Eco-design targets • No involvement of management (high & middle management)	• No use of Eco-design tools
2	• Eco-design practices and tools are applied ad hoc, to fix a specific problem or to accomplish a specific task, but without formalization and systematization • Eco-design strategy set (high level) • Eco-design is pushed by support functions (e.g.: HSE)	• The tools allow the Eco-design approach of at least one life cycle step of the product • The tools are generic • The tools provide guidance regarding current regulations and future short-term regulations • The tools do not allow a quantified approach for each project

	• Responsibility of support functions (e.g.: HSE) & involvement of high managers • Some tools / guides are used	
3	• Eco-design practices are applied in some specific sectors (e.g.: CMC, analytical department) and/or phases (e.g.: phase 2a) of the R&D processes, but without strategic control and monitoring • Eco-design is pushed by development teams and support functions help them (e.g.: HSE) • Rules / procedures /standards implemented	• The tools allow the Eco-design of several life cycle steps of the product • The tools are developed and/or adapted to fulfil the development team's needs & constraints • The tools provide guidance regarding future mid-term regulations • The tools allowed quantified approach •
4	• Eco-design practices are applied within the different R&D functions and process phases, in a formalized and controlled way • Eco-design is pushed by the Business • Responsibility shared within all activities • Tools and guidelines widely used	• The tools allow the Eco-design of the product life cycle from Cradle-to-grave • The tools are developed and/or adapted to fulfil the external stakeholders' expectations • The tools provide guidance regarding future long-term regulations • The tools allowed a systemized quantified approach
5	• Eco-design practices are applied during all of the development process of a drug, in a systemic, holistic and collaborative way. R&D process stakeholders are trained and are aware of the environmental impacts of their product and processes • Environmental parameters are embedded at the same level as economic, safety for the patient, quality aspects	• The tools allow a global Eco-design appraoch, not only focused on environmental aspects, but also on the economy, safety, etc

Appendix 19

User tests, results & calculation

Scoring of the different users

From one (fully disagree) to seven (fully agree)	User 1	User 2	User 3	User 4	User 5	User 6	User 7
1. Overall, I am satisfied with how easy it is to use this system.	6	6	6	6	5	7	4
2. It is simple to use this system.	6	6	6	6	5	6	5
3. I can effectively complete my work using this system.	6	7	6	5	6	6	3
4. I am able to complete my work quickly using this system.	6	7	6	5	6	7	3
5. I am able to efficiently complete my work using this system.	6	6	6	5	6	6	3
6. I feel comfortable using this system.	6	7	5	6	5	6	3
7. It was easy to learn to use this system.	7	7	6	6	6	7	6
8. I believe I became productive quickly using this system.	7	6	6	6	5	6	5
9. Whenever I make a mistake using the system, I recover easily and quickly.	6	6	5	4	6	7	5

10. The information (on-screen messages, documentation) provided with the system is clear.	7	6	5	4	4	7	5
11. It is easy to find the information I need.	7	7	6	5	4	6	5
12. The information provided with the system is easy to understand.	6	6	5	4	5	6	5
13. The organization of information in the system is clear.	6	7	6	5	6	5	5
14. The interface of the system is pleasant.	6	7	6	6	5	6	5
15. I like using the interface of this system.	7	6	6	6	4	6	5
16. This system has all the functions and capabilities I expect it to have.	6	6	5	4	4	5	5
17. Overall, I am satisfied with this system.	6	7	6	6	6	7	4

Calculation

$$Satisfaction\ level\ (\%) = \frac{\sum users\ scorings}{Score\ \max \times n_{users} \times n_{statement}}$$

Description	Value
$\sum users\ scorings =$ Score S1 for user 1 + Score S1 for user 2 + … + Score S1 for user 6 + … + Score S17 for user 7	673
Score max = highest score to be set by one user for one statement	7
n_{users} = number of users in the study	7
$n_{statement}$ = number of statements to assess	17

Appendix number 20

List of excipients used for the marketed mAbs

Excipient	CAS number	Number of marketed forms with the excipient	% of marketed forms with the excipient
Water for injection	7732-18-5	188	79%
Polysorbate 80	9005-65-6	154	64%
L-Histidine	71-00-1	111	46%
Sucrose	57-50-1	94	39%
L-Histidine hydrochloride monohydrate	5934-29-2	81	34%
Polysorbate 20	9005-64-5	64	27%
Sodium chloride	7440-23-5	62	26%
Sodium hydroxide	1310-73-2	51	21%
Trehalose dihydrate	6138-23-4	43	18%
Citric acid	77-92-9	35	15%
Acetic acid	64-19-7	33	14%
Sodium citrate dihydrate	6858-44-2	33	14%
Hydrochloric acid	7647-01-0	30	13%
L-Methionine	63-68-3	26	11%
EDTA	6381-92-6	25	10%
L-Arginine	74-79-3	22	9%
Mannitol	69-65-8	21	9%
Sorbitol	50-70-4	20	8%
Sodium acetate trihydrate	6131-90-4	16	7%
Glycine	56-40-6	12	5%
Sodium Phosphate, Monobasic	10049-21-5	12	5%
Succinic acid	110-15-6	9	4%
Disodium phosphate dihydrate	10028-24-7	8	3%
L-Proline	147-85-3	8	3%
Sodium dihydrogen phosphate dihydrate	13472-35-0	8	3%
Sodium phosphate dibasic heptahydrate	7782-85-6	8	3%
Trisodium citrate dihydrate	6132-04-3	7	3%
Poloxamer 188	9003-11-6	6	3%
Adipic acid	64-19-7	5	2%
dibasic sodium phosphate heptahydrate	7782-85-6	5	2%
Sodium phosphate	7601-54-9	5	2%
Disodium hydrogen phosphate anhydrous	7558-79-4	4	2%
Disodium phosphate dodecahydrate	10039-32-4	4	2%
hyaluronidase (human recombinant)	757971-58-7	4	2%
Sodium dihydrogen phosphate monohydrate	10049-21-5	4	2%
Disodium succinate hexahydrate	6106-21-4	3	1%

D-sorbitol	50-70-4	3	1%
L-Aspartic acid	56-84-8	3	1%
L-Glutamate	142-47-2	3	1%
Pentetic acid	67-43-6	3	1%
Potassium chloride	7440-09-7	3	1%
Potassium dihydrogen phosphate	7778-77-0	3	1%
Calcium acetate	62-54-4	2	1%
L-Lysine, Hydrochloride	657-27-2	2	1%
Macrogol	25322-68-3	2	1%
Nitrogen	7727-37-9	2	1%
Sodium acetate	127-09-3	2	1%
1, 1, 3, 3-propane tetraphosphonic acid, tetrasodium salt, dihydrate (PTP)	119733-46-9	1	0,4%
2-(N-morpholino) ethane sulfonic acid (MES)	4432-31-9	1	0,4%
Dextran 40	3371-50-4	1	0,4%
Diethylenetriaminepentaacetic acid	67-43-6	1	0,4%
Human Serum Albumin	70024-90-7	1	0,4%
Maltose	133-99-3	1	0,4%
Monosodium glutamate	142-47-2	1	0,4%
Sodium dihydrogen phosphate, anhydrous	7558-80-7	1	0,4%
sodium phosphate dibasic dihydrate	10028-24-7	1	0,4%
Sodium phosphate, dibasic	7558-79-4	1	0,4%
Stannous chloride dihydrate	10025-69-1	1	0,4%
Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride)	1185-53-1	1	0,4%
Tromethamine	77-86-1	1	0,4%
Anhydrous sodium succinate	150-90-3	1	0,4%

Appendix number 21

Suggestions of the levels, for each dimension, that could be formalized in further research

	Soft side	Macro	Meso	Micro
Level 1	• Environmental considerations are linked to the own value of the employees • External stakeholders are not considered	• No strategy	• Practices and tools not implemented within development teams • No involvement of management	• No quantified approach • Tools answer regulatory concerns
Level 2	• Sensibilization are performed • Employees are aware of the Eco-design challenges • External stakeholders are	• Strategy set at high level (e.g.: Sustainable leader in the field)	• Eco-design practices and tools are applied ad hoc • Eco-design is pushed by one function in the company • Responsibility of Eco-design delegate to one function	• Tools consider one life cycle step • Generic tools used • Tools do not allow quantified approach
Level 3	• Trainings are performed • Clients and consumers are sensibilize regarding Eco-designed products • Partnerships with stakeholders of the value chain are engaged, without a systemic manner (e.g.: share of LCA results on demand)	• Quantified strategy set with a date (e.g.: reduction of the carbon	• Eco-design practices applied by key functions without strategic control and monitoring • Eco-design is pushed by development teams • Rules / procedures/ standard are implemented	• Tools consider several steps of the life cycle • Tools allow quantified approach

Level 4	• Partnerships with stakeholders of the value chain are engaged, with a systemic manner (e.g.: elementary flow of LCA dataset shared for each product supplied)	• Each management layer of the company has objectives related to Eco-design	• Eco-design practices are applied by concerned functions in a formalized and controlled way • Eco-design is pushed by business teams	• Tools consider the whole life cycle • Tools allow a systemized quantified approach
Level 5	• The environmental aspects are fully embedded in the mindset of the employees • Cross sectorial partnerships are engaged • The company contribute to the Eco-design knowledge within the community	• Strategy is intrinsically part of the business model and plan of the company • Eco-design embedded at the same level as economic, quality parameters	• Eco-design practices applied by the whole organization • Systemic, holistic, and collaborative approach	• Tools allow optimization and integrate other aspects such as economy, safety