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Methodological Framework for Life Cycle Assessment in the Pharmaceutical Sector

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Abstract

Besides their indisputable positive health effects, pharmaceutical residues in the environment are identified to also have potential adverse effects on wildlife and human beings. They may enter environmental compartments (e.g. surface water bodies) through different pathways, such as excretion and a subsequent insufficient waste water treatment. Manufacturing predominantly in low-cost countries with inadequate environmental regulations and an increased use of pharmaceuticals on a global scale further aggravates the environmental relevance of the pharmaceutical sector.

To comprehensively identify potential environmental impacts of pharmaceuticals and to establish measures to effectively reduce them, a life cycle perspective is imperative. For this purpose, life cycle assessment (LCA) is the predominant methodology since it is internationally standardized and widely applied among different sectors. Due to its broad use, however, individual methodological specifications are also necessary for particular product groups which can be formulated as Product Category Rules (PCR) according to ISO 14025 and ISO/TS 14027. For pharmaceuticals, such harmonized specifications do not exist which leads to a high level of methodological inconsistency between existing LCA studies. Moreover, case studies from the pharmaceutical sector often focus on manufacturing processes, whereas the use and end-of-life (EoL) stage are excluded from the assessment.

The goal of this thesis is therefore to develop a scientifically robust, comprehensive and yet applicable methodological framework to guide LCAs of pharmaceutical products and processes and, in the long term, to harmonize and thus facilitate the future application of the LCA methodology in the pharmaceutical sector. To this end, two research questions are formulated: How should a LCA framework for pharmaceutical products be outlined to provide methodological guidance on sector-specific questions and challenges (RQ.1) and how can life cycle stages beyond the manufacturing stage of pharmaceuticals be modeled (RQ.2)?

First, a review on existing generic LCA standards and guidelines on PCR development, sector-specific LCA guidelines, PCRs and LCA case studies on pharmaceutical products is conducted to identify methodological differences, similarities and open gaps. Furthermore, the review provides a structural basis for the framework development. Based on this, either new rules are drafted (e.g. a classification scheme of pharmaceutical products based on their functionality, the definition of product system, system boundaries and functional unit (FU), guidance on impact assessment) or existing methodological specifications are adopted if there is already a high consensus on these rules among literature (e.g. regarding general data quality requirements). As one major gap in existing studies, the exclusion of the use and EoL stage is identified which is of particular importance since most of the pharmaceutical emissions are expected to occur here. Therefore, a life cycle inventory model is

developed to estimate emissions of Active Pharmaceutical Ingredients (API) during and after use of a pharmaceutical. To this end, API flows and emissions for different galenic formulations are compiled and quantification approaches as well as potential data sources are presented. All results are finally applied in a case study on an ibuprofen analgesic from cradle to grave. The LCA study reveals that the manufacturing stage is the largest contributor to all environmental impacts, whereas the share of the use and EoL stage to the overall environmental impacts is insignificant. Even though a systematic review of the framework´s applicability and completeness are beyond the scope of the case study, it discloses some methodological and practical challenges, such as the general comparability of pharmaceuticals, how positive effects of pharmaceuticals could be integrated into the damage-oriented LCA, the expansion of system boundaries to include Research and Development (R&D) activities and other processes along the healthcare pathway or the transferability of the rules to veterinary medicine. The most limiting factor is indubitably the availability of consistent data. This affects not only the life cycle inventory but also calculations on an impact assessment level. Therefore, future research should focus on both, the further development of the framework as well as provision of comprehensive data.

Yet, the methodological framework presented in this thesis significantly refines the LCA methodology for pharmaceuticals and allows a more comprehensive environmental assessment from cradle to grave with only few data which are usually publicly available. Hence, current environmental assessment approaches for pharmaceuticals are expanded by a more holistic perspective.

Keywords: Pharmaceuticals, Life Cycle Assessment, Harmonization, Product Category Rules, Use, End-of-Life

List of publications

I. Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Harmonized rules for future LCAs on pharmaceutical products and processes**. Int J Life Cycle Assess **24**, 1040-1057, published 2019, Springer Nature. https://doi.org/10.1007/s11367-018-1549-2

II. Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment**. Int J Life Cycle Assess **25**, 1436-1454, published 2020, Springer Nature. https://doi.org/10.1007/s11367-019-01722-7

III. Siegert M.-W., Saling P., Mielke P., Czechmann C., Emara Y., Finkbeiner M. **Cradle-to-grave life cycle assessment of an ibuprofen analgesic**. Sustainable Chem. Pharm. **18**, 100329, published 2020, Elsevier B.V.. https://doi.org/10.1016/j.scp.2020.100329

List of abbreviations

ABPI	Association for the British Pharmaceutical Industry
ACS GCI	American Chemical Society Green Chemistry Institute
API	Active Pharmaceutical Ingredient
AR	Absorption Rate
ATC	Anatomic Therapeutic Chemical
BRA	Benefit-Risk Assessment
CF	Characterization Factor
DALY	Disability-Adjusted Life Years
DDD	Defined Daily Dose
DF	Distribution Factors
EC	European Commission
EF	Effect Factor
EMA	European Medicines Agency
EoL	End of Life
EPD	Environmental Product Declaration
EphMRA	European Pharmaceutical Market Research Association
EPS	Eco-Pharmaco-Stewardship
ER	Excretion Rate
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
FU	Functional Unit
GMP	Good Manufacturing Practices
GPCRD	Guidance for Product Category Rule Development
GWP	Global Warming Potential
HALY	Health-Adjusted Life Years
IES	International EPD System
ISO	International Organization for Standardization

LADME	Liberation-Absorption-Distribution-Metabolism-Excretion
LCA	Life Cycle Assessment
LCI	Life Cycle Inventory
LCIA	Life cycle Impact Assessment
LEX	Life Expectance at Birth
MEC	Measured Environmental Concentration
MR	Metabolization Rate
MSDS	Material Safety Data Sheet
NNH	Number Needed to Harm
NNT	Number Needed to Treat
O	Objective
PCR	Product Category Rules
PEC	Predicted Environmental Concentration
PEF	Product Environmental Footprint
PMI	Process Mass Intensity
PoE	Point of Emission
PSCI	Pharmaceutical Supply Chain Initiative
QALY	Quality-Adjusted Life Years
QSAR	Quantitative Structure-Activity Relationship
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
R&D	Research and Development
RQ	Research Question
SATP	Standard Ambient Temperature and Pressure
SLCA	Social Life Cycle Assessment
TP	Treatment Period
TR	Technical Report
TS	Technical Specifications

WHO	World Health Organization
WWTP	Waste Water Treatment Plant
YLD	Years of Life Disabled
YLL	Years of Life Lost

Contents

1 Introduction

We know not only since the Covid-19 pandemic starting in 2020 that a modern society in a globalized world strongly depends on a nationwide yet affordable supply with pharmaceutical products.

The United Nations report that the world population has increased between 1990 and 2015 from 5.3 billion to 7.3 billion, and is expected to further grow up to 9.7 billion in 2050 (United Nations 2020a). One major reason for this development is an improved medical supply, especially in developing countries (WHO 2020). With a growing world population, upon reversion, the demand for and use of pharmaceutical products further increase. Hence, the revenues of the worldwide pharmaceutical market between 2001 and 2018 grew from 390.2 to 1,204.8 billion U.S. dollars (IQVIA 2019).

But there is also a rising concern about the environmental impacts of pharmaceuticals (Bound et al. 2006). Does the end justify the means?

1.1 Theoretical background and motivation

The economic growth of the pharmaceutical sector, on the one hand, contributes to the achievement of the third sustainable development goal 'good health and wellbeing' which aims at providing a better access to medicine and vaccine (United Nations 2020b), but it also leads to some overarching observations with potential environmental relevance on both, production- as well as consumption-related dimensions:

The increased demand for pharmaceuticals leads to higher production volumes. Thus, more resources are necessary for the manufacturing processes, and rising emissions occur from the production even though some pharmaceutical manufacturing sites made improvements with regard to resource efficiency and emission control. However, most of the production of active pharmaceutical ingredients (API) are produced in countries, such as Pakistan, China and India, where no proper legislation exists to prevent (non-) pharmaceutical emissions to the environment. These emissions can lead to severe environmental problems, such as the development of resistant germs (Ashfaq et al. 2017; Bu et al. 2013; Fick et al. 2009).

Furthermore, many (particularly developing) countries do not have a proper waste water treatment or waste management infrastructure. With an increasing consumption of pharmaceutical products, more untreated (or insufficiently treated) waste water, feces and urine which contain active pharmaceutical ingredients as well as their metabolites can be released to the environment. In addition, there is a higher risk for more unused pharmaceuticals to be improperly discarded which can also boost the release of APIs to environmental compartments, such as soil or water bodies (Quadra et al. 2019; Rivera-Jaimes et al. 2018).

Environmental sustainability in the context of pharmaceutical products, however, is often separately discussed and practiced for products and manufacturing processes without depicting their interrelations. Starting from the Green Chemistry Principles (Anastas and Eghbali 2010), existing environmental assessment approaches (so called 'green metrics') such as the E-factor (Sheldon 2005) or process mass intensity (PMI) (Jiménez-González et al. 2012) are mainly manufacturing-oriented and describe the relation between generated waste (E-factor) or input material such as solvents and reagents (PMI) to the mass of desired product. The environmental risk assessment (ERA) for medicinal products, on the contrary, only considers the potential risk for aquatic and terrestrial eco systems by the use and release of an API without taking a manufacturing perspective into account. The assessment is based on usage data, as well as physico-chemical, ecotoxicological and fate properties of the substance (EMA 2018).

These approaches are insufficient to comprehensively assess the environmental impact of a pharmaceutical product since they only consider a particular section within the life cycle which can lead to deceptive conclusions:

For instance, 'greener' pharmaceuticals are mostly developed to decrease residues of APIs in the environment, e.g. by increasing their biodegradability (Kümmerer and Hempel 2010). But most of these studies do not take the environmental burden of the production stage into consideration and vice versa (Kümmerer 2009). However, this is crucial to avoid that a better biodegradability is achieved at the expense of a higher environmental burden during the production stage.

Another example for a potential environmental blow back is the implementation of take-back scheme for unused or expired pharmaceutical waste to reduce API emissions from improper disposal of pharmaceutical waste via sinks or toilets. Even though API-emissions can be significantly reduced by this, this measure potentially leads to higher non-API emissions due to increasing transportation activities (Cook et al. 2012).

These observations reveal the importance of considering all API- and non-API-emissions among the entire life cycle of a pharmaceutical, i.e. from API production, galenic formulation and packaging to distribution, application and end-of-life treatment (excretion and/or disposal), to effectively curb its potential environmental impacts (Caldwell et al. 2016). This need is already outlined in the 'Strategic Approach to Pharmaceuticals in the Environment' by the European Union and also mentioned by several initiatives, such as the ACS GCI Pharmaceutical Roundtable (Bryan et al. 2018), the Pharmaceutical Supply Chain Initiative (PSCI) (PSCI 2019) or the Eco-Pharmaco-Stewardship (EPS) Initiative (EFPIA 2015).

However, the assessment of pharmaceuticals according to specific environmental criteria is neither yet implemented in the guidelines for good manufacturing practices (GMP), nor germane for the authorization of pharmaceuticals for human use (in contrast to veterinary medicine) (Fabrega and Carapeto 2020).

To achieve a life cycle-oriented evaluation of the potential environmental impacts of pharmaceutical products, life cycle assessment (LCA) can be applied. This widely used method allows to determine the environmental profile of products and services from a holistic perspective, i.e. from resource extraction to the use and final disposal (Finkbeiner 2013). LCA can be used to identify environmental hotspots and optimization potentials within the value chain, to compare products or process alternatives, or for marketing purposes. It is internationally standardized by the ISO 14040 series on LCA and contains four phases (ISO 2006b, 2006c):

1. Goal and scope definition:
In the first phase, the intended application and audience, as well as drivers for conducting the study are described. It also covers fundamental methodological choices, such as system boundaries, data requirements or the definition of a functional unit (FU) (i.e. the quantified performance of a product system).

2. Inventory analysis:
In the second phase, qualitative and quantitative information on all inputs and outputs is collected for the entire product system. This data includes flows such as resources, energy, auxiliaries, by-products, waste, or emissions.

3. Impact assessment:
In the third phase, inventory data are assigned to an impact category such as climate change (classification) and converted to impact assessment results through scientific models which represent the cause-effect chain for a certain environmental impact (characterization). This is conducted for all substances that cross the system boundaries by leaving or entering the environment (elementary flows).

4. Interpretation:
The last phase aims at discussing the results from the second and third phase with regard to the goal and scope definition. This iterative process can reveal necessary adjustment to be made within the LCA study.

Existing LCA-related ISO standards, technical specifications (TS) and reports (TR) provide generic principles, requirements and guidance. However, they also consign a high degree of freedom to

practitioners since they are formulated in a way to cover all products and services and therefore, do not contain any product-specific information or method adjustments.

In order to complement and harmonize the LCA methodology, e.g. for certain industries, different forms of additional guidelines and standards exist. These documents provide further detailed information and methodological requirements for a particular sector or product group, and aim at increasing the reliability and comparability of LCA studies. This is particularly indispensable if LCAs are published and used for communication purposes. It can also decrease the complexity of the LCA method for users and increase the potential field application of LCA in the particular sector, e.g. by facilitating the comparison of products. As one example, Product Category Rules (PCR) can be applied to this end.

According to ISO TS 14027, PCR are a 'set of specific rules, requirements and guidelines for developing Type III environmental declarations and footprint communications for one or more product categories', whereas a product category is defined as a 'group of products that can fulfil equivalent functions' (ISO 2017). Most of the PCR publishers (so called 'program operator') provide both, general instructions which are valid among all product categories, as well as separate product (sub-) group specific guidance documents. For some product categories, however, various PCR from different program operators exist with significant differences regarding their quality, scope and level of detail. Therefore, a harmonization of PCR is further required.

As an example, the PCR Guidance Development Initiative published a Guidance for Product Category Rule Development (GPCRD) to supplement existing LCA standards and provide further recommendations on PCR development (GPCRD 2013). Similarly, the Product Environmental Footprint (PEF) by the European Commission (EC) provides generic guidance in conjunction with specifications for certain product categories (Lehmann et al. 2016).

Taking this into account, a harmonized product-specific framework in the form of a PCR provides not only important specifications and further methodological guidance for a product group, but also reveals the potential to facilitate the application of LCA in a particular sector.

1.2 Research gaps and challenges

PCR are already applied in many sectors, particularly in the building and construction industry (Minkov et al. 2015). In the pharmaceutical sector, however, only one PCR for vaccines for human and veterinary medicine exists which expired by the end of 2018 (IES 2014). So far, only one LCA study in the form of an environmental product declaration (EPD) on the veterinary vaccine IMPROVAC® (Pfizer 2012) has been published based on this PCR.

Other related guidance documents are either generic, i.e. not product group-specific, or focus on single environmental impacts (e.g. the Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices (NHS 2012)).

Besides their limited use, the comparison of these documents also reveals some methodological issues which are, however, essential for the application of LCA. For instance, the FU in existing LCA studies is mostly mass-based (e.g. the production of 1 kg API) which appears to be feasible if the emphasis is on the manufacturing process. For the assessment of products, however, the FU, which is defined as the 'quantified performance of a product system', should somehow reflect the intended function (i.e. the therapeutic purpose) of a pharmaceutical. This is particularly inevitable if the environmental profiles of product alternatives with the same indication are compared.

Other examples for important, yet insufficiently addressed methodological specifications in the context of pharmaceutical products are the definition of system boundaries, selection of pharma-specific/relevant impact categories and the consideration of the use and end-of-life (EoL) stage which is usually excluded in existing studies (Emara et al. 2019).

This lack of methodological guidance leads to several challenges regarding the implementation of LCA in the pharmaceutical sector:

Despite the pertinence of life cycle thinking in the pharmaceutical industry, LCA is not frequently used in the sector (Emara et al. 2018). Due to a **lack of methodological harmonization**, existing LCA case studies on pharmaceuticals are hardly comparable with regard to their results and scientific quality. Usually, a conformity with existing standards or guidelines is not explicitly stated. Furthermore, LCA requires an enormous effort to obtain qualitative and quantitative data for the product system. Therefore, simplified screening applications such as the PMI-LCA tool by the ACS GCI Pharmaceutical Roundtable (ACS GCI 2021) or the ABPI blister pack carbon footprint tool by the Association for the British Pharmaceutical Industry (ABPI) (ABPI 2021) have been published. Some companies also developed streamlined in-house LCA solutions (e.g. the GlaxoSmithKline GSK guides for solvent and reagent selection (Adams et al. 2013; Jimnez-Gonzlez et al. 2004)). However, these solutions are often confidential and partially exclude life cycle stages or processes which are not directly related to the own business activities. Hence, **further guidance is needed to facilitate the data collection step as part of the Life Cyle Inventory (LCI)** and consequently, to reduce the amount of work for LCA practitioners without limiting the scope of the study.

Current studies strongly **focus on the manufacturing processes** that are operated by the process owner without including product characteristics. The scope of these studies is usually

limited to a particular manufacturing step which is assessed by comparing different production technologies or improvement measures, whereas the pharmaceutical product itself and its potential environmental impact are not considered. Hence, they **lack in connecting the production with the consumption-related processes** of environmental relevance.

To address these challenges, a methodological framework is needed which is complementary to existing standards and guidelines but includes and, if necessary, further specifies product-related information.

1.3 Structure of the thesis

This work consists of five chapters (see Figure 1):

First, the theoretical background as well as the motivation for this research are presented in the 'introduction' chapter. This section also includes current research gaps and related challenges.
Second, the 'research approach' to tackle the aforementioned gaps and challenges is presented. This chapter contains the goal of the thesis, research questions and objectives. Furthermore, the relation between these aspects and the three publications is illustrated.
Third, the publications are presented in the 'results' chapter. Each publication is briefly introduced and the respective results of each publication are outlined. The supplementary materials of each publication are listed in the Appendix.
Fourth, the key findings of the thesis are summarized in the 'discussion' chapter. In addition, remaining and new scientific challenges are depicted. To this end, methodological and application-related aspects are reflected.
Fifth, important findings of this work as well as recommendations with regard to future research activities are explained in the 'conclusion and outlook' chapter.

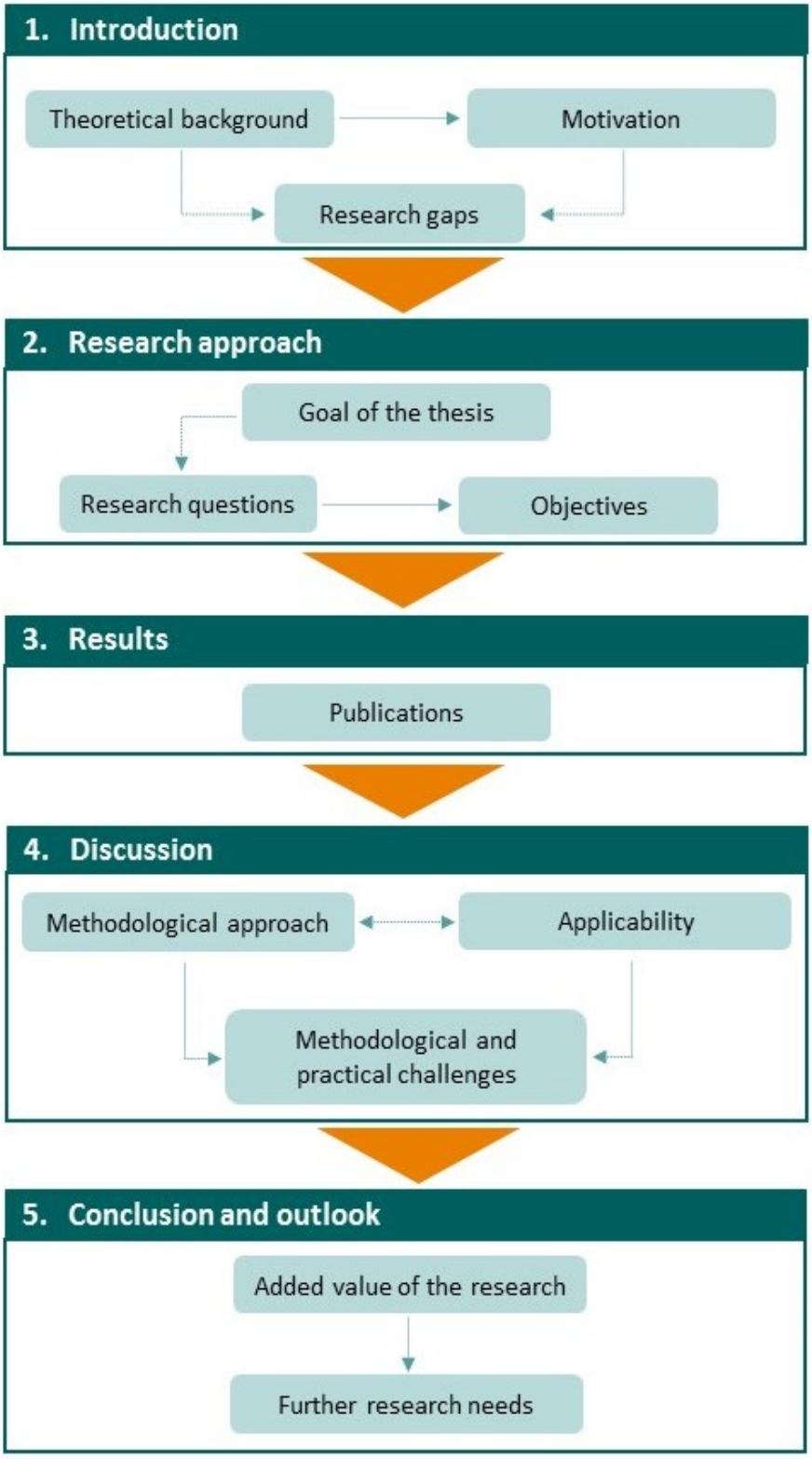

Figure 1: Structure of the thesis

2 Research approach

In this chapter, the overall goal of the thesis and the related research questions are presented. Furthermore, specific objectives are defined and the connection to the publications is illustrated.

2.1 Goal of the thesis, research questions and objectives

The goal of the thesis is to develop scientifically robust and comprehensive yet applicable rules to guide LCAs of pharmaceutical products and processes. Such rules are necessary to harmonize and thus facilitate the future application of the LCA methodology in the pharmaceutical sector.

Two research questions (RQ) are therefore defined to specify how this overall goal can be achieved:

- **RQ.1: How should a LCA framework for pharmaceutical products be outlined to provide methodological guidance on sector-specific questions and challenges?**
  The first research question addresses the general structure and content of an LCA framework for pharmaceuticals to enhance the harmonization of the LCA method for this particular product group.

- **RQ.2: How can life cycle stages beyond the manufacturing stage of pharmaceuticals be modeled?**
  The second research question relates to the modelling of the use and EoL stage of pharmaceuticals, i.e. the intake, behavior in the human body, excretion to the WWTP or direct emission to the environment, the behavior in the WWTP and finally, the emission to water bodies.

To answer these research questions, they are further divided into specific objectives (research targets) O.1.1-O.1.2 (RQ.1), O.2.1-O.2.2 (RQ.2) and O.3 (crosscutting RQ.1 and 2):

- O.1.1: Determination of the structural and content-related frame (i.e. definition of the product category and subcategories based on a classification scheme, differentiation between generic and specific rules (granularity) and content structure)

  O.1.2: Specification of the methodological requirements for performing LCA on pharmaceutical products (e.g. system boundaries and functional unit)

- O.2.1: Identification of API flows and emissions during the use and EoL of pharmaceuticals for the most common galenic formulations

  O.2.2: Development of calculation approaches to quantify API flows and emissions occurring during/from the use and EoL of pharmaceuticals

- O.3: Application of the preliminary work in a case study

These research questions and objectives are addressed in the three publications. Their relation is further explained in the following chapter.

2.2 Relation between publications, objectives and overarching methodology

The core of this thesis consists of three peer-reviewed journal publications (see List of publications). Their individual contribution to answer the research questions, the relation to the corresponding objectives and the interlinkage between the publications are presented in this chapter:

I. Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Harmonized rules for future LCAs on pharmaceutical products and processes.** Int J Life Cycle Assess **24**, 1040-1057 (2019). https://doi.org/10.1007/s11367-018-1549-2

The scientific purpose of this publication is twofold: First, it provides a generic structure of the framework (O.1.1) which comprises a definition of the product category, a proposal to cluster pharmaceuticals in corresponding product subcategories and an overview (table of content) of methodological requirements which have to be determined for pharmaceutical products. To this end, the concept of granularity is introduced, i.e. some rules apply to all pharmaceutical produces, whereas some subcategories may require specific rules.
Second, harmonized rules are presented (O.1.2) based on the structural frame by reviewing and combining sector-specific LCA guidance documents with generic guidelines on PCR development and other approaches such as the product environmental footprint (PEF).

This publication therefore contributes to answer RQ.1 by concatenating structural specifications with methodological results in terms of harmonized rules which are incorporated into the framework.

II. Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment.** Int J Life Cycle Assess **25**, 1436-1454 (2020). doi: https://doi.org/10.1007/s11367-019-01722-7

The exclusion of the use and end-of-life stage is identified as one of the biggest gaps in existing LCA studies. The second publication addresses this issue by determining all potential API emissions and flows occurring from/within the use and EoL stage for the most prominent galenic formulations (O.2.1). Subsequently, a simplified quantification model for these API emissions and flows is presented (O.2.2). To this end, pharmacokinetic information is

combined with existing approaches (e.g. from risk assessment), studies and tools. It is then exemplarily tested for ibuprofen as a proof of concept.

This publication addresses RQ.2 by systematically compiling API flows and emissions for different intake scenarios depending on the galenic formulation, and linking this qualitative information to a quantitative inventory model for the use and EoL stage. Since the model can be seen an integral part of the framework, the publication also contributes to meet O.1.2.

III. Siegert M.-W., Saling P., Mielke P., Czechmann C., Emara Y., Finkbeiner M. **Cradle-to-grave life cycle assessment of an ibuprofen analgesic.** Sustainable Chem. Pharm. **18**, 100329 (2020). https://doi.org/10.1016/j.scp.2020.100329

The third publication complements the research approach by combining the findings obtained from the first two publications: The harmonized rules as well as the model for the use and EoL stage are applied in this cradle-to-gate case study on an ibuprofen-based analgesic (O.3). Even though a systematic test of the framework is not the focus of the third publication, the case study also allows to evaluate the practicability of the framework. However, this is also further discussed in chapter 4.2.

Figure 2 summarizes the relations between the publications, the objectives, the research questions and the overall goal.

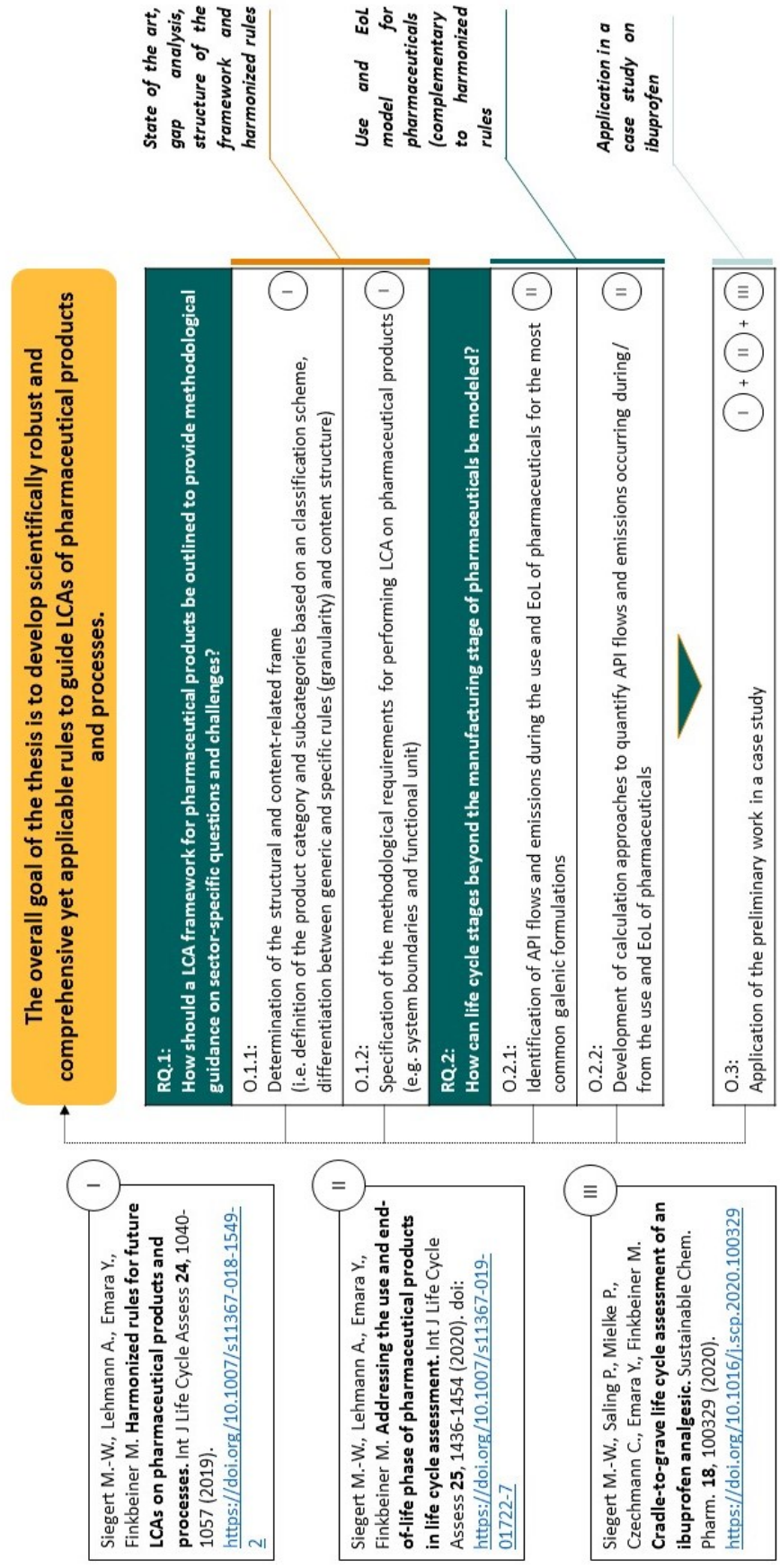

Figure 2: Link between the publications and the overall goal, research questions and objectives

3 Results

The core of this thesis consists of three publications which are the main outcome of the research conducted with regard to the overall goal, research questions and objectives. In the following, each publication is summarized and presented in separate subchapters.

3.1 Harmonized rules for future LCAs on pharmaceutical products and processes

This chapter contains the following publication:

- Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Harmonized rules for future LCAs on pharmaceutical products and processes**. Int J Life Cycle Assess **24**, 1040-1057 (2019). https://doi.org/10.1007/s11367-018-1549-2

In this publication, the potential structure and content of harmonized rules to conduct LCA in the pharmaceutical sector are compiled and discussed. To cover a broad spectrum of pharmaceutical products but also considering characteristics of certain pharmaceutical groups, we differentiate between generic ('horizontal') and specific ('vertical') rules. Generic rules are expected to be applicable for all pharmaceutical products, whereas specific rules depend on the therapeutic purpose of the pharmaceutical product under study.

To address objectives O.1.1-O.2.2, a systematic bottom-up approach is utilized: generic standards and guidelines on PCR development are reviewed and complemented by information obtained from sector-specific guidelines, PCRs and LCA case studies on pharmaceutical products. Hence, the new rules are supposed to be in alignment with existing work but also provide more detailed information and close methodological gaps if necessary. Based on the review, the structure (i.e. elements that need to be included in a PCR for pharmaceutical products) and content (i.e. description of the aforementioned elements/rules) are determined. In particular, the definition of the 'product category' according to ISO 14025 and ISO/TS 14027 (ISO 2006a, 2017), elements of the goal and scope phase as defined in ISO 14040 and 14044 (ISO 2006b, 2006c), information on the life cycle inventory and other aspects (e.g. additional environmental information as part of Type III environmental declarations) are taken into account. Considering the structure of the rules and the definition of a product category by ISO 14025, two different product categories are introduced in the publication: Pharmaceuticals for human use as defined by the European Union (European Union 2001) (on a generic level) and pharmaceutical subcategories that fulfill the same therapeutic purpose according to the World Health Organization´s 'Anatomic Therapeutic Chemical (ATC)' classification scheme (WHO 2017) (on a specific level).

Afterwards, a selection of rules which appear to be pharma-specific and pivotal methodological requirements for future pharma-LCAs are presented in this publication, namely rules for the product

system and system boundaries, the functional unit, the use and EoL stage, impact assessment and additional information. These rules are part of the later published 'Product Category Rules (PCR) for pharmaceutical products and processes'[1] (Siegert et al. 2019a) (see also Appendix A.4.). Within the PCR for pharmaceutical products and processes, the methodological requirements described in the first publication have been integrated. However, some minor changes have been made due to new findings (e.g. regarding the use and EoL stage) or practical causes. For transparency reasons, these deviations are presented in Appendix A. 1. Comparison of the Draft PCR and final framework.

As the original publication was issued in 2018, additional recently published literature which could serve as input to the PCR development has been identified.

While the PCR on vaccines for human or veterinary medicine by the International EPD system (IES 2014) expired in 2018, one new sector-specific guideline and seven additional LCA case studies on pharmaceutical products has been published and identified since.

The potential impacts of these additionally identified documents on the results presented in this publication are addressed in chapter 4.1.1.

[1] This document is licensed under a Creative Commons Attribution 4.0 International License. It has not been peer reviewed by a third party and thus, does not meet the official requirements for cumulative dissertations according to § 2 Abs. 2 PromO by TU Berlin. Therefore, it is not listed under 'list of publication'.

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HEALTHCARE

Harmonized rules for future LCAs on pharmaceutical products and processes

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Abstract

Purpose The manufacturing of pharmaceuticals and their occurrence in the environment generated growing concerns of stakeholders. Life Cycle Assessment (LCA) is a suitable tool to identify potential environmental impacts within the whole pharmaceutical value chain. However, existing pharma-LCAs revealed several methodological shortcomings and challenges. To support the development of future LCAs in the sector, draft Product Category Rules (PCR) for pharmaceuticals for human use and their manufacturing processes are proposed.

Methods Existing LCA case studies were evaluated and compared based on the methodological requirements according to the ISO 14044 standard. In addition, PCRs from the pharmaceutical sector, generic LCA standards, and product-specific guidelines were reviewed. Subsequently, overlaps between and deviations from these sources were identified. It was determined whether methodological requirements can be adopted from existing standards and guidelines or whether additional rules or specifications for pharmaceutical products are needed.

Results and discussion The overall PCR structure was established in alignment with ISO 14044, ISO TS 14027, and the Guidance for PCR development (GPCRD). For the definition of product groups, the third level of the Anatomic Therapeutic Chemical (ATC) classification system was determined as appropriate level of detail (granularity). The methodological requirements, e.g., the definition of goal and scope, inventory analysis, as well as the impact assessment, were set considering the intended application and the product system. However, the majority of these proposed methodological requirements go beyond current practice in existing pharma-LCAs (e.g., definition of an effect-based functional unit). Moreover, the need for specific rules depending on the active pharmaceutical ingredient (API), the galenic formulation, and regional aspects was described and discussed.

Conclusions This work tackles current methodological challenges of LCA application in the pharmaceutical sector by providing harmonized rules to guide future studies on pharmaceutical products and processes. However, modelling the use- and end of life phase as well as considering pharma-specific impacts were revealed as remaining challenges.

Keywords Environmental product declaration · Harmonization · Life cycle assessment · Pharmaceutical processes · Pharmaceutical products · Product category rules

1 Introduction

1.1 Background

1.1.1 Pharmaceuticals in the environment

The use of pharmaceuticals enables an increasing life expectancy of human beings and is therefore essential for the well-being of a growing and ageing global population (Taylor

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2015). This leads to an increasing demand for pharmaceutical products. In the period of 2001 to 2015, the revenue of pharmaceutical products increased from 390 to 1072 billion USD (BPI n.d.). At present, 4000 active pharmaceutical ingredients (APIs) are administered worldwide (Weber et al. 2014).

However, there is a growing concern about possible adverse effects of pharmaceutical substances in the environment (e.g., Roig and D'Aco 2015; Williams et al. 2016). Since improved access to healthcare services and pharmaceutical products leads to an increasing production volume, pharmaceutical compounds pose a higher risk to the environment (Weber et al. 2014; Arnold et al. 2014).

APIs can enter the environment through excretion, disposal of unused medicinal products in sinks and toilets, or can be directly released from manufacturing facilities (Weber et al. 2014; Straub 2016; Kümmerer 2009; Rehman et al. 2015). Additional emission pathways are caused by using sewage sludge or manure as fertilizer (Klatte et al. 2016). Therefore, residues of various pharmaceutical substances and their metabolites were found in different concentrations (ng/L to μg/L) in various environmental compartments such as soil, groundwater, surface water, and drinking water (Gilroy et al. 2014; Li 2014; Roig and D'Aco 2015; Larsson 2014). Moreover, they can cause severe environmental problems through toxicological effects in non-target organisms (Du et al. 2016; Gamarra et al. 2015; Winker et al. 2008; Escher et al. 2011; Christen et al. 2010). Numerous studies describe these potential adverse effects on specific species and ecosystems (e.g., Ford and Fong 2016; Watanabe et al. 2016; Isidori et al. 2006).

As there is still a lack of comprehensive monitoring strategies, knowledge on exact quantities of pharmaceuticals entering the environment, and long-term studies on ecological risks caused by pharmaceutical substances (Roig and D'Aco 2015), it is an emerging issue for politics and science (Weber et al. 2014; Kümmerer 2008).

In addition to these potential API emissions to the environment, other direct and indirect emissions related to the manufacturing processes of pharmaceutical products (e.g., due to energy use) can occur. To address these issues, pharmaceutical companies have made significant efforts during the last decades to analyze potential environmental impacts caused by their products and manufacturing processes.

1.1.2 Environmental assessment in the pharmaceutical industry

Thus far, different green metrics are used in the pharmaceutical sector to quantify the environmental performance on a product or process level, e.g., E-factor (Sheldon 2005), Process Mass Intensity (Jimenez-Gonzalez et al. 2011), and Green Aspiration Level (Roschangar et al. 2015). However, these metrics are based on mass efficiency and do not include a comprehensive assessment of the full life cycle (Ott et al. 2014). This is also reflected by current practices in the pharmaceutical industry that primarily aim at improving manufacturing processes, e.g., by substituting reagents, solvents, and catalysts with more environmentally friendly alternatives, using continuous processes instead of multistep batch-processes, or by implementing energy saving and waste reduction programs (Adams et al. 2013; Banimostafa et al. 2015; Bryan et al. 2013; Ciriminna and Pagliaro 2013; Jiménez-González and Overcash 2014). In order to environmentally evaluate these process optimization concepts, "greener" drug designs, and for avoiding burden shifting, a holistic view on the life cycle impacts of a pharmaceutical product is indispensable (EEA 2010; McElroy et al. 2015; Kümmerer 2007; Slater and Savelski 2009). Life Cycle Assessment (LCA) is a widely accepted method defined by international standards and guidelines that can be applied to identify potential environmental impacts within the whole value chain (Finkbeiner et al. 2006; Kralisch et al. 2015).

However, despite the generally accepted importance of the life cycle perspective to comprehensively evaluate potential environmental impacts of the pharmaceutical products and manufacturing processes, LCA application is still not widespread in the pharmaceutical sector due to different reasons (Jiménez-González and Overcash 2014). In particular, the lack of methodological harmonization within the sector (e.g., choice of an appropriate functional unit), low availability of inventory data, e.g., due to confidential synthesis routes, and complex supply chains are the biggest bottlenecks leading to methodological inconsistencies within the existing pharma-LCAs (Kralisch et al. 2015; Jiménez-González and Overcash 2014; Jiménez-González et al. 2004; De Jonge 2003). To overcome these obstacles, some companies developed streamlined in-house solutions to perform simplified LCA studies and to quantify the environmental performance of their manufacturing processes, e.g., Fast Life Cycle Assessment of Synthetic Chemistry (FLASC) Tool (Curzons et al. 2007). However, detailed information on these solutions (e.g., content of internal databases) are usually confidential and publicly not available. Thus, harmonized and scientifically robust rules are needed to complement existing approaches and to further promote the application of LCA within the pharmaceutical sector.

1.2 Goal and scope

The aim of this paper is to provide consistent, harmonized rules to conduct LCA studies within the pharma sector. These rules serve as technical input to draft Product Category Rules (hereinafter called draft PCR) for pharmaceutical products and manufacturing processes. We differentiate between so-called generic rules and specific rules. Generic rules are intended to be valid for all pharmaceutical products and manufacturing processes. They are complemented by

specific rules, which may be needed for predefined subcategories (e.g., migraine drugs). To propose a directly applicable PCR intended to be published by a specific program operator goes beyond this work. However, such future PCRs can be developed based on the technical content provided in the draft PCR. This intends to facilitate the practical application of LCA and type III environmental product declarations according to ISO 14025 in the pharmaceutical industry.

The need for harmonization is already emphasized by different publications (e.g., Jiménez-González and Overcash 2014; Kralisch et al. 2015). Additionally, De Soete et al. (2017), Raju et al. (2016b), and Tufvesson et al. (2013) discuss and propose some methodological requirements for pharma-LCAs based on literature reviews and stakeholder surveys which were also considered in the current work. However, these publications do not include and describe the elements required for a PCR in detail. Hence, the overall goal of developing a draft PCR for pharmaceutical products and processes is achieved by considering the following research questions:

- Which methodological requirements need to be defined (general structure)?
- How broad or narrow should the product category be determined (granularity)?
- How can applicable, yet scientifically robust methodological requirement be defined (content)?

This paper focuses on pharmaceuticals for human use only. Thus, the product category includes substances which are intended to cure, mitigate, or prevent human diseases or symptoms or are administered to restore, correct, or influence the physiological functions through a pharmacological, immunological, or metabolic effect, or to make a medical diagnosis (European Union 2001). Personal care products, food supplements, medical devices, bulk chemicals, and veterinary medicine are not explicitly considered. However, some of the results presented here could be also applicable for or transferable to such similar product groups.

2 Methods

A bottom-up approach (see Fig. 1) is used following the recommendations for PCR development provided in existing standards (ISO 2017; 2006a) and guidelines (GPCRD 2013):

First, a review of existing generic standards and PCR guidelines, sector-specific guidelines, and PCRs is conducted. Furthermore, LCA case studies in the sector are identified and reviewed with regard to methodological requirements as defined by the ISO 14040/44 standard (ISO 2006b, c). According to the ISO 14027 (ISO 2017), they can be used as supporting LCA studies within a PCR preparation process.

The documents have a different level of detail and thus differ regarding their scope of application, e.g., setting generic LCA standards for products and services (e.g., ISO 2006c), describing LCA requirements for a specific sector (e.g., WBCSD 2014) or addressing single environmental impacts for a certain product group (e.g., NHS 2012). Therefore, they address partly common and partly complementary aspects which served as input for defining the methodological requirements within the draft PCR.

Subsequently, these sources are analyzed with regard to PCR-specific information and methodological requirements according to ISO 14040/44. Furthermore, it is examined whether methodological requirements can be adopted or new product-specific rules are required.

Apart from the research steps described above, an interdisciplinary dialogue of experts from industry, science, politics, and non-governmental organizations is applied. The methodological proposals and challenges are discussed in half-yearly, regular meetings.

The following subsections describe the procedure of reviewing generic standards (2.1.1), sector-specific guidelines (2.1.2), existing PCRs (2.1.3), as well as existing pharma-LCAs (2.2).

2.1 Review of generic standards, sector-specific guidelines, and existing PCRs

Existing LCA-based environmental information and PCRs need to be revised before developing new PCRs to reduce differences in the underlying rules for future pharma-LCA studies and thus to increase the consistency between the studies (ISO 2017; GPCRD 2013). For this purpose, we conducted a review on generic LCA standards and guidelines, sector-specific guidelines, and existing PCRs for pharmaceutical products.

2.1.1 Generic standards and guidelines

The purpose of reviewing generic standards and guidelines was twofold. First, the standards and guidelines are used to establish a structural basis for the draft PCR. Thus, formal requirements for a future public PCR are met. Second, they provide generic information on methodological requirements, e.g., data quality, which can be included in the draft PCR. In particular, the ISO standards on LCA (ISO 2006b, c) were considered which define the principles and framework of the LCA methodology (Finkbeiner et al. 2006). In addition, the ISO standard for environmental labels and declarations (ISO 2006a) was taken into account. Furthermore, Ingwersen and Subramanian (2014) propose the Guidance for Product Category Rule Development (GPCRD) as an appropriate guidance to develop PCR. These documents are complemented by the Technical Specification for Environmental labels and declarations—Development of

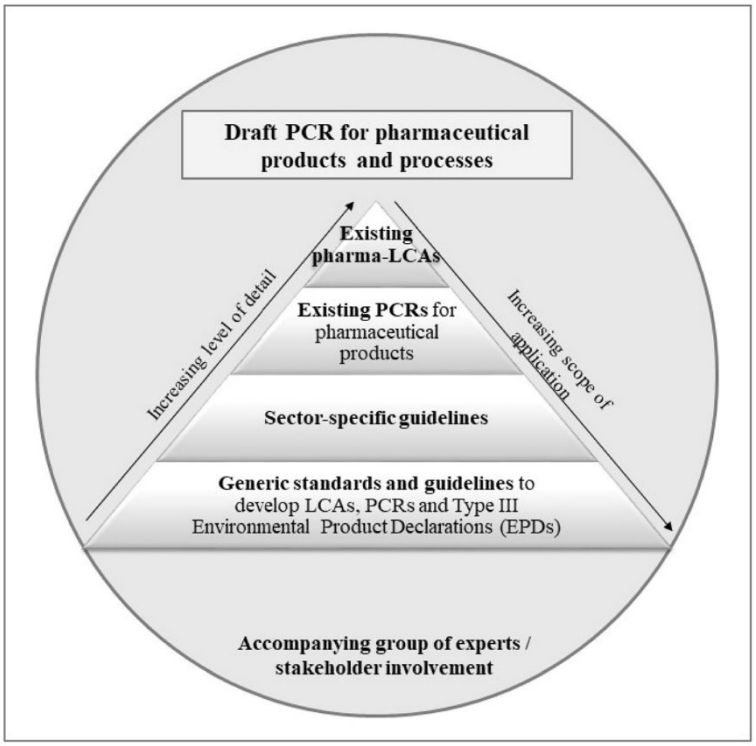

Fig. 1 Approach to develop a draft PCR for pharmaceutical products and processes

product category rules (ISO 2017). Finally, the Guidance for Product Environmental Footprint Category Rules (PEFCR) as a European approach (European Commission 2017) which provides detailed methodological rules to increase the comparability of products (Finkbeiner 2014; Lehmann et al. 2016) was also considered.

2.1.2 Sector-specific guidelines

Sector-specific guidelines are usually based on existing LCA standards and provide more detailed, complementary methodological requirements for the LCA of single products or product categories within a sector (e.g., information on product-specific databases). To identify currently applicable guidelines, references within the publications taken from the literature research were used. Additionally, the accompanying group of experts from the pharmaceutical and chemical industry was consulted. However, the number of sector-specific guidelines is limited. The National Health Service developed the "Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices" (NHS 2012) based on the "GHG Protocol Product Life Cycle Accounting and Reporting Standard" (GHG 2011). Furthermore, another guidance was published by the NHS on appraising sustainability of care pathways (NHS 2015). In addition, the World Business Council for Sustainable Development (WBCSD) published the "Life cycle metrics for chemical products" which was used to determine requirements for modelling production processes of precursor chemicals (WBCSD 2014).

2.1.3 Existing product category rules

The relevant ISO standards emphasize the need of alignment of PCRs for the same product category (e.g., ISO 2006a, 2017). The PCR developer should consider the adoption of these PCRs to facilitate harmonization between existing rules (ISO 2006a). Therefore, we investigated if PCRs for pharma-relevant product categories already exist. Based on an overview of existing PCR programs published by Minkov et al. (2015), online databases with PCRs provided by different program operators were searched for "pharmaceuticals," "pharmaceutical products," and "medicine" to identify existing PCRs for pharmaceutical products. However, only one PCR for pharmaceuticals, namely for vaccines, has been developed by the International EPD®System (IES 2014). The PCR is based on the requirements given in "PCR Basic Module, CPC Division 35: Other chemical products; man-made fibres" (IES 2015) and the "General Program Instructions" (GPI) (IES 2017) published by the same program operator. Following the definition of the European Union (2001), vaccines are pharmaceutical products. The existing PCR, however, cannot just be adopted due to its

limitation to immunological products. Additionally, the PCR is also applicable for veterinary medicine which is not within the scope of this work. Nevertheless, some elements and information within the existing PCR were used to develop the new draft PCR.

2.2 Review of existing pharma-LCAs

Any PCR should be based on existing LCA studies which are in accordance with the ISO 14040 series (ISO 2006a, 2017). Furthermore, ISO (2017) states that these so-called supporting LCAs shall represent all life cycle stages of a product within the product category covered by the PCR. Additionally, GPCRD (2013) requires that the functional unit (FU) used in the supporting LCA studies (called "underlying LCA" in the GPCRD) shall be applicable to the PCR. Nevertheless, we decided to take all LCAs within the scope, i.e., case studies of pharmaceutical products (pharmaceutical intermediates, APIs or final drugs, incl. packaging) for human use into account, whether or not a conformity with ISO 14040 series is clearly stated or life cycle stages are excluded. LCAs of chemicals (e.g., solvents) were only included if application in a pharmaceutical product system is clearly stated. However, LCAs in a green chemistry context or with regard to other aspects of the healthcare sector (e.g., medical devices, surgical tools) are not considered. Moreover, the search thus excluded studies on environmental toxicology, environmental risk assessments, as well as publications related to green metrics, methods, and tools.

The literature review was conducted without restriction on the publication date using Google scholar with predefined terms such as "Life cycle assessment," "LCA," "Environmental Product Declaration," and "Footprint" combined with "pharmaceutical" or "fine chemical." Furthermore, references within the studies meeting the scope and existing reviews by Tufvesson et al. (2013), Raju et al. (2016b), and De Soete et al. (2017) were considered. Subsequently, the studies have been analyzed following the goal and scope phase according to ISO 14040/44. The goal and scope definition covers the majority of the methodological requirements within an LCA, whereas some PCR-specific aspects, e.g., definition of an appropriate product category, are not described by the ISO 14040 series. The goal and scope phase includes the following methodological requirements: goal, product system and system boundaries, functional unit, allocation (method), impact categories, impact assessment method, assumptions, data requirements, data collection, data calculation and use of methods and tools, normalization, grouping, weighting, and interpretation.

Since the type of critical review and the format of the report as elements of the scope definition are not product group-specific, they were not considered within the review of existing pharma-LCAs.

Following the procedure described in the previous section, 37 LCA case studies on pharmaceutical products and processes were identified in publically available sources (e.g., peer-reviewed journals) to this date.

2.3 Draft PCR development

To determine the methodological requirements that are needed in the draft PCR, the results of the literature review (see Table 1) were analyzed and compared according to the following aspects:

- Definition of a product category
- Elements of the goal and scope phase (according to ISO 14040/44)
- Information on the life cycle inventory (especially regarding the use- and end of life phase)
- Others (e.g., ISO conformity, temporal/ geographic scope, additional environmental information)

Then, overlaps, agreements, differences, and gaps between them were identified by cross-comparison. Subsequently, we examined whether some of the methodological requirements can be adopted from existing standards and guidelines (e.g., requirements that are not pharma-specific such as general data quality requirements) or whether additional rules or specifications for pharmaceutical products are required.

Table 1 summarizes all documents used to develop the draft PCR.

3 Results and discussion

This section provides information on general aspects, i.e., structure (3.1), granularity of the product category, description of the product group and classification (3.2), as well as product group-specific methodological requirements proposed for the draft PCR (3.3).

3.1 Structure of the draft PCR

The general structure of the draft PCR presented in Table 2 is in alignment with the ISO standards, i.e., it consists of the methodological requirements according to the goal and scope phase within ISO 14044 (see 2.2 section) which are complemented by PCR-specific aspects (e.g., product classification, temporal and geographic scope) according to GPCRD (2013).

The structure of the draft PCR is applicable for both pharmaceutical products and processes. However, for a future adoption of the PCR by a program operator, the order of the (sub-) sections of the draft PCR may need to be adjusted.

Table 1 Documents used to develop the draft PCR for pharmaceutical products and processes

Type of document	Reference
Generic standards and guidelines	▪ ISO 14025 (ISO 2006a) ▪ ISO 14040/44 (ISO 2006b, c) ▪ ISO TS 14027 (ISO 2017) ▪ Guidance for Product Category Rule Development (GPCRD) (GPCRD 2013) ▪ Product Environmental Footprint Category Rules Guidance (PEFCRG) (European Commission 2017)
Sector-specific guideline	▪ GHG Protocol Product Life Cycle Accounting and Reporting Standard (NHS 2012) ▪ Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices (NHS 2015) ▪ Life Cycle Metrics for Chemical Products (WBCSD 2014)
Existing PCR	▪ PCR for Vaccine for human or veterinary medicine, whether or not put up as medicaments (IES 2014)
Existing LCA studies	▪ Pharma-LCAs in accordance with the scope of this paper (Amado et al. 2017; Belboom et al. 2011; Bruggink and Nossin 2006; Brunet et al. 2014; Bunnak et al. 2016; Cespi et al. 2015; Cook et al. 2012; De Jonge 2003; De Soete et al. 2013, 2014a, b; Henderson et al. 2008; Jiménez-González 2000, 2004; 2013; Jödicke et al. 1999; Kim et al. 2009; Lee et al. 2016; Llano 2012; Mata et al. 2012; McAlister et al. 2016; Nielsen et al. 2007; Ott et al. 2014, 2016; Pietrzykowski et al. 2013; Poechlauer et al. 2010; Ponder and Overcash 2010; Raju et al. 2016a, b; Ramasamy et al. 2015; Raymond et al. 2010; Sherman et al. 2012; Van der Vorst et al. 2009, 2011, 2013; Wernet et al. 2010; Yaseneva et al. 2016)

3.2 Granularity, product category, and classification

The level of detail, i.e., the granularity of the product category, should be determined in a way that allows to cover a broad set of products with the PCR (GPCRD 2013). However, PCRs shall be defined for a group of products which have an equivalent or similar function (ISO 2006a). Here, the granularity of the draft PCR is determined with regard to two different levels:

- Level I: Generic ("horizontal") rules for all pharmaceutical products

  These rules apply for all pharmaceuticals for human use according to the definition of the European Union (2001) and their manufacturing processes to provide technical guidance on integrating sector-specific aspects into the LCA study.

  To classify the product category, the Central Product Classification (CPC) System by the United Nations is applied, namely the subdivision 3526 as "medicaments, for therapeutic or prophylactic uses" (United Nations 2015). This classification system is recommended by the PCR Guidance Development Initiative and is already applied by certain program operators (e.g., International EPD®System). However, the UN CPC classification system does not differentiate between pharmaceuticals for veterinary medicine or human use. Additionally, API-specific aspects or the pharmacological and therapeutic mode of action are not reflected. Therefore, a second level is developed to provide more specific rules for product subcategories having the same therapeutic function.
- Level II: Specific ("vertical") rules for pharmaceutical products

  These specific rules apply for pharmaceuticals for human use which are clustered in therapeutic subcategories based on their medical function.

  To determine and classify the product subcategories, the "Anatomic Therapeutic Chemical" (ATC) classification system is applied. Based on expert knowledge, the third level of the ATC scheme enables a proper determination of therapeutic classes. Therefore, APIs with identical third level ATC code can be summarized in specific subcategories due to their equivalent functionality (e.g., migraine drugs, ATC code N02C). For these subcategories, more specified rules can possibly be derived or may be even needed to enable consistent comparability.

Table 2 Structure of the draft PCR for pharmaceutical products and processes

Table of contents
1. General information (e.g., validity (temporal, geographic), conformity with other standards, product category and classification)
2. PCR review and background information (e.g., existing PCR for product category and supporting LCA studies)
3. Goal and scope (e.g., goal of the study, functional unit, content declaration and product system)
4. Inventory (e.g., requirements for primary and secondary data, specifications regarding use- and end of life phase)
5. Impact assessment (e.g., definition of impact categories and impact assessment methods)
6. Results and interpretation (e.g., description and interpretation of results)
7. Additional information (e.g., side effects)

The classification scheme is used by the World Health Organization (WHO) and allows describing APIs with regard to their medical and chemical properties. APIs are classified on five different levels: The anatomical main group (first level) describes the organ that is affected, whereas the second and third levels represent therapeutic/pharmacological subgroups. Furthermore, the fourth and fifth levels describe the chemical properties of the API (WHO 2017). However, the definition of an appropriate categorization level that considers the therapeutic or pharmacological function of a product is a challenging task. De Soete et al. (2017) describe that participants of their survey do not believe in product categories for pharmaceuticals. Nevertheless, we are convinced that the third level of the ATC classification scheme can be utilized to define subcategories for pharmaceutical products and therefore to compare APIs in an LCA context based on their pharmacological function although this structure requires a detailed knowledge of pharmacological characteristics of each subcategory. Using the third level of the ATC classification scheme leads to over 300 subcategories which probably need specifications. However, this draft PCR does not define specific rules for each subcategory but indicates the need of further specification if this is required.

The granularity of the draft PCR as well as the product classification for pharmaceutical products and processes is illustrated in Fig. 2.

The distinction between different levels of details is already used by the European Commission as well as existing program operators by providing generic rules for all product groups and complementary requirements for a specific product category, e.g., PEFCR guidance by European Commission (2017) or PCR Basic module for other chemical products; man-made-fibres by IES (2015).

Within the draft PCR, however, the rules for drug manufacturing processes can be seen as an integral part of the generic rules for pharmaceutical products. To our knowledge, a specification of rules on a third level and the definition of a separate product classification on a process level is strongly related to the chemical sector and therefore beyond the scope of this work.

3.3 Methodological requirements

For some methodological requirements within the draft PCR, rules according to existing standards or guidelines, e.g., ISO 14044, are adopted (e.g., general data quality requirements). In this paper, however, only selected product group-specific methodological aspects of the draft PCR are presented which have emerged as pharma-specific, controversial, or novel aspects, namely product system and system boundaries (3.3.1), functional unit (3.3.2), use- and end of life phase (3.3.3), impact assessment (3.3.4), and additional information (3.3.5). At the beginning of each subsection, the proposed rules for pharmaceutical products are highlighted. Additionally, information on the following questions is provided:

- Is there a need to adjust the proposed rule depending on the scope of the study, i.e., assessment of pharmaceutical products or manufacturing processes?
- Is a specification of the rules generally recommended (according to level II of the draft PCR)?
- Is there a need to specify the rules depending on the goal and intended application of the study, i.e., external or internal application, comparison of different products/processes, or hot spot analysis of one product/process?

Afterwards, each proposed rule is explained in more detail and discussed with regard to its applicability as well as the current practice in existing pharma-LCAs.

3.3.1 Product system and system boundaries

The proposed rules are

- *A cradle to grave analysis shall be conducted*

  - **Applicable for:** Pharmaceutical products
  - **Specific rules recommended:** No
  - **Depends on goal/intended application:** No

- *A cradle to gate analysis (i.e., cradle to API, cradle to galenic form, or cradle to preparation) shall be conducted*

  - **Applicable for:** Pharmaceutical processes
  - **Specific rules recommended:** No, if products are identical
  - **Depends on goal/intended application:** No

The definition of the product system is independent of the therapeutic subcategory or the intended application. It includes the specification of the system boundaries, a creation of a system diagram to illustrate the product system in a comprehensive way, and a description of each life cycle stage. Depending on the scope of the study, however, two different system boundaries are defined:

1. A full cradle to grave analysis shall be performed to assess the environmental impacts on a product level including all activities (e.g., energy supply, manufacturing of basic chemicals and auxiliary products, transportation, treatment of production waste, and expired/unused pharmaceuticals) and devices (e.g., syringes to administer vaccine) needed to perform the function of the pharmaceutical product.

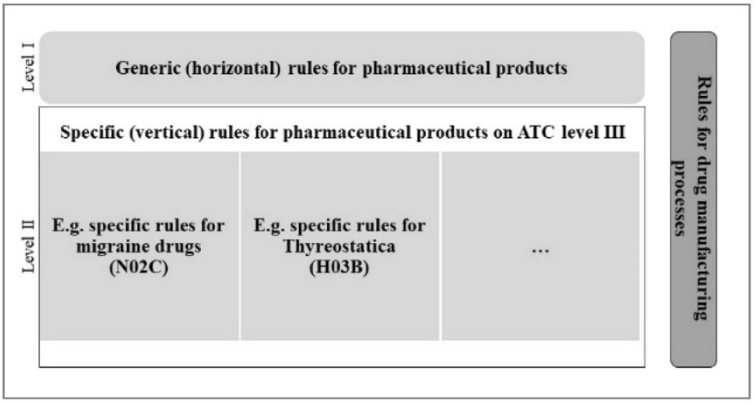

Fig. 2 Granularity of the draft PCR for pharmaceutical products and processes

2. If a life cycle study focusses on comparing or analyzing pharmaceutical manufacturing processes (e.g., compare different process designs to produce an identical API or drug), the system boundaries shall be cradle to gate including the waste streams generated during the production. If products are identical, it is assumed that changes in the process have no influence on the use- and end of life phase.

In general, cut-offs should be minimized. But due to practical and consistency reasons, the amount of required data can be reduced by applying cut-off criteria. For this purpose, environmental significance according to ISO (2006c) shall be applied as a cut-off criterion. Hence, cutting off small amounts of chemical substances with a high toxicity is avoided.

Most of the existing pharma-LCAs were intended to optimize the design of pharmaceutical manufacturing processes and address potential positive and/or adverse effects to the environment due to changes in the production chain of pharmaceuticals (e.g., Mata et al. 2012; Jiménez-González et al. 2004; Poechlauer et al. 2010; Bunnak et al. 2016; Ramasamy et al. 2015; Ponder and Overcash 2010; Bruggink and Nossin 2006). But despite the increasing evidence of toxic impacts on non-target organisms (Kümmerer and Hempel 2010), current LCA studies in the pharmaceutical sector usually assess potential environmental impacts within cradle to gate or gate to gate-system boundaries. However, the exclusion of downstream processes, i.e., use- and end of life phase, can possibly result in misleading conclusions. This is why we propose here—contrary to existing practice—to consider the whole life cycle on a product level.

In addition, the product system shall be divided into upstream ("cradle to gate"), core ("gate to gate"), and downstream ("gate to grave") processes. A clear description of the system boundaries is substantial for defining the methodological requirements within the draft PCR, e.g., to decide which processes require primary data. However, current terminology in existing pharma-LCAs regarding system boundaries does not sufficiently describe the details of production chains in the pharmaceutical sector. According to IES (2014), API production, galenic formulation, and packaging are elements of the core system which describes gate to gate boundaries. But these production steps are often performed by different companies. Thus, these processes can also belong to the upstream or downstream system depending on the commissioner of the study. To address this, the cradle to gate boundaries for upstream processes were specified as "cradle to API," "cradle to galenic form," and "cradle to preparation" to avoid confusion what the "factory gate" in this context actually means (see Fig. 3). These specific boundaries shall be also considered if the core and downstream processes are defined. For instance, if the study is performed by a company that only produces an API, the API production shall be defined as the core system whereas the production of basic chemicals is part of the upstream system. The galenic formulation, packaging, distribution, as well as the use- and end of life phase, however, belong to the downstream system.

Different system boundaries were also mentioned by existing publications, e.g., "cradle to pharmacy" (De Soete et al. 2013) or "cradle to patient" (Pfizer 2012).

The overall product system includes all life cycle stages of a pharmaceutical product, whereas the boundaries of upstream, core, and downstream system shall be defined specifically as described above.

3.3.2 Functional unit

The proposed rules are

- *The functional unit shall be defined as the "treatment of [one or more] [child(ren) or adult(s)] in [geographic region] with [disease/indication] for [period of application]" (effect-based FU)*

– **Applicable for:** Pharmaceutical products

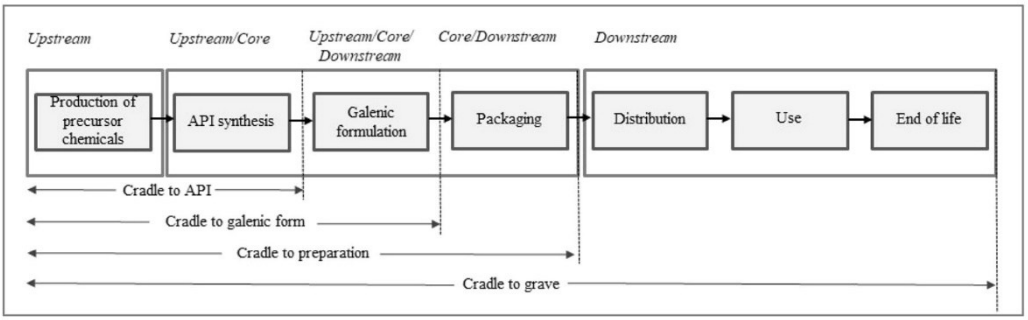

Fig. 3 Generic life cycle of a pharmaceutical product

- **Specific rules recommended:** Yes
- **Depends on goal/intended application:** Yes, if the goal of the study is to perform a hot spot analysis or to identify optimization potentials

- *The functional unit shall be defined as the "production of [x] kg API" or "production of [x] defined daily dose(s) (DDD)" (mass-based FU)*

- **Applicable for:** Pharmaceutical processes
- **Specific rules recommended:** No, if product properties are identical
- **Depends on goal/intended application:** No

The functional unit is defined as the quantified performance of a product system. We propose two different functional units, depending on the scope of the study:

If the study is intended to analyze a production process and identify optimization potentials within, or compare different manufacturing processes within cradle to gate-system boundaries, a mass-based FU (also known as "declared unit" (European Commission 2017; GPCRD 2013; ISO 2017)), e.g., "production of X kg API" or "production of DDD" shall be used. This rule is independent of the goal or intended application. A further specification of the functional unit is not needed if the processes produce a product with identical properties. In this case, the reference flow is identical with the functional unit. However, this functional unit needs to be modified if a study is intended to assess the potential environmental impacts on a product level.

For pharmaceutical products, an effect-related FU, i.e., treatment of an average patient in a specific geographic region with a certain disease (indication) for a prescribed application period, shall be applied to perform the environmental assessment of a pharmaceutical product within cradle to grave boundaries. This is required to enable a fair comparison of different APIs based on their pharmacological properties. The reference flow is the required DDD, i.e., the amount of API that is needed to fulfill the therapeutic purpose over a predefined period and, if needed, medical devices to administer the drug. This choice, however, depends on the goal and intended application of the study. If the study is intended to internally analyze hot spots or to identify optimization potentials, a mass-based functional unit on a product level could also be applied.

However, the need to extend the mass-based functional unit is also emphasized by De Soete et al. (2017). For this purpose, the patient (adult or child), geographic scope, medical indication, and duration of the medicinal treatment shall be taken into account and specified depending on the API that is considered:

The patient shall be specified due to differences regarding the DDD for adults and children. Additionally, the geographic scope shall be indicated to consider geographic differences in terms of access to medical treatment, distribution of pharmaceuticals, state of the art of wastewater treatment plants (WWTP), and disposal routes of municipal and industrial waste.

Furthermore, the disease needs to be clearly defined to ensure comparability between the products. Pharmaceuticals may have multiple functions and pharmacological applications. For instance, acetylsalicylic acid can be used as a stomatological product, but it also has an antithrombotic effect (WHO 2017). To this end, the third level of the ATC classification scheme shall be utilized within the FU definition to describe the medicinal indication, i.e., the functional unit shall be specified for each subcategory considering the corresponding field of application. The ATC classification scheme assigns unique ATC codes to APIs depending on its therapeutic function. Consequently, one API with various fields of applications has different ATC codes. Thus, using the third level of the ATC helps to define the therapeutic purpose of the API considered in the study and therefore avoid confusion about other possible applications of the API. Furthermore, multiple pharmacological effects are addressed within "additional information" (see section 3.3.5).

Finally, the duration of the medicinal treatment shall be defined to determine the reference flow, i.e., the amount of API or final preparation that is applied to treat the disease. However, it should be considered that the duration of the

medicinal treatment can differ significantly depending on whether it is a chronic condition or an acute disease. Therefore, the type of disease shall be investigated and taken into account when defining the goal and scope of the study (see section 3.4.2).

Again, this proposed rule differs from existing practice. The majority of existing pharma-LCAs exclude the function of the product. Therefore, a mass-based functional unit without time reference, e.g., the production of 1 kg or 1 mol API or a relation to the pharmacological function of the drug, is usually applied (e.g., Raymond et al. 2010; Van der Vorst et al. 2011; De Soete et al. 2014a). Thus, the product itself and the pharmacological function or medical indication play a minor role in existing LCA studies from the pharmaceutical sector. As this is not seen as appropriate, we propose to apply an effect-based FU if the study is intended to analyze a pharmaceutical product.

3.3.3 Use- and end of life phase

The proposed rules are

- *The use- and end of life phase shall be considered in the study and is based on simplified models applying average data (e.g., metabolization and excretion rate) or rather different use- and end of life scenarios. The use phase shall include the distribution to hospitals or pharmacies and the intake of the pharmaceutical product by the patient. The end of life phase shall consider the excretion depending on the galenic formulation and emission of the API to the WWTP, as well as the disposal of expired and unused drugs (including packaging).*

– **Applicable for:** Pharmaceutical products
– **Specific rules recommended:** Yes
– **Depends on goal/intended application:** No

- *The use- and end of life phase may be excluded*

– **Applicable for:** Pharmaceutical processes
– **Specific rules recommended:** No, if products are identical
– **Depends on goal/intended application:** Yes

The use phase of a pharmaceutical product includes the transport from factory gate, distribution via pharmacies and hospitals, patient travel, intake, and use of devices to administer the drug. The end of life stage covers the excretion of the API, emission to the WWTP, and the effluent to the environment. This is illustrated by a simplified model (see Fig. 4).

Additionally, the waste treatments of packaging, unused/expired pharmaceuticals, and residues from the WWTP are included. However, other elements of the healthcare pathway according to De Soete et al. (2017) and NHS (2015) that are not directly linked to the product category (e.g., medical devices and surgery activities) are not covered by this draft PCR.

The choice of considering the downstream life cycle stages on a process level depends on the scope and intended application of the study:

If an LCA is intended to analyze a production process or to compare two different manufacturing processes, the use- and end of life phase can be excluded due to practical reasons, if a change of process parameters within the core system does not affect the downstream processes or if these processes are identical. Thus, a specification of this rule on a process level is not necessary. However, according to the ISO 14040 series, the use- and end of life phase can only be excluded if these stages are expected to be environmentally insignificant or information on these stages are not available. But the potential ecotoxicological effects of pharmaceuticals are indicated by numerous studies (see section 1.1.1). Therefore, the overall downstream processes shall be included, if potential environmental impacts on a product level are assessed. This is independent of the goal or intended application of the study. Nevertheless, in practice, only a few existing pharma-LCAs (e.g., Cook et al. 2012; Sherman et al. 2012) took the effects of API emissions into account. This is one of the most significant gaps in existing LCA practice in the pharma sector.

If included, a life cycle inventory model for the use- and end of life phase is needed in the first place. For this purpose, the pharmacokinetic behavior of an API in the body, from metabolism to excretion, needs to be considered. In addition, information on the different emission pathways depending on the galenic formulation, data on the occurrence of metabolites or transformation products, average consumption and disposal data, API-specific removal rates and information on the fate between sewage sludge and effluent within the WWTP based on empirical data, as well as waste treatment options for pharmaceuticals need to feed into such a model.

But to date, only few simplified models for the use- and end of life phase of pharmaceuticals are already published (e.g., Ortiz de García et al. 2013), whereas a comprehensive, yet applicable inventory model in an LCA context for estimating relevant flows of pharmaceuticals in the downstream phase does not yet exist.

In addition, the lack of empirical data due to an insufficient systematic measurement of API concentrations at WWTP effluents or in the natural environment is another obstacle to model the downstream phase even though this data would prove very useful for a comprehensive environmental assessment along the life cycle of pharmaceutical products. Therefore, the use- and end of life phase

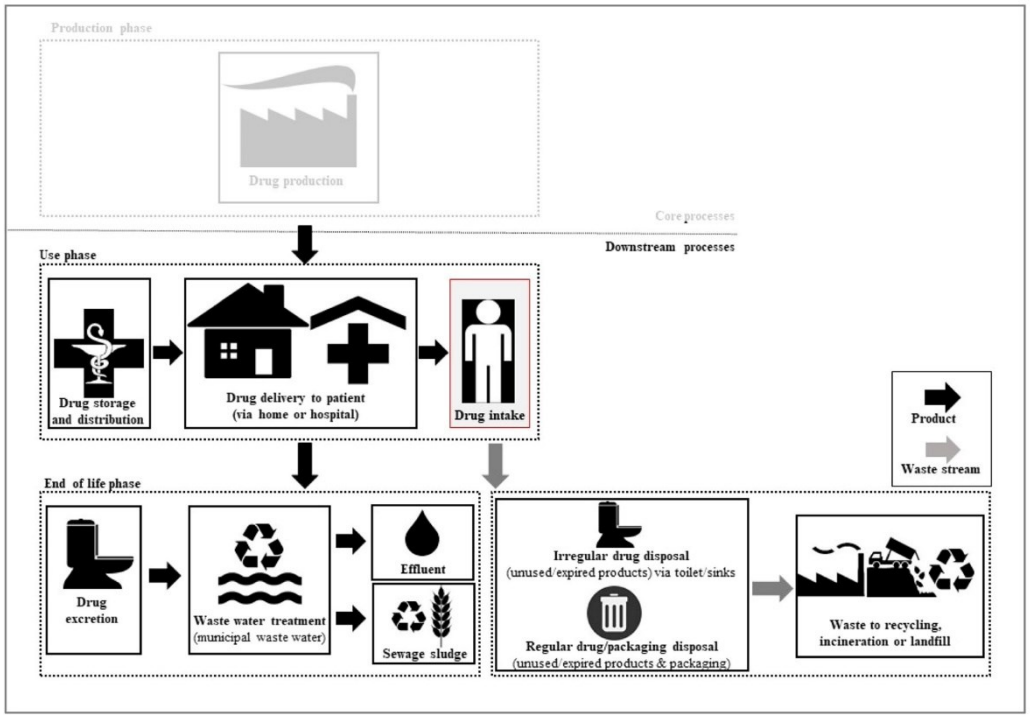

Fig. 4 Use- and end of life phase of pharmaceuticals (simplified model)

can only be calculated based on simplifying assumptions, e.g., regarding the metabolism of human beings. To this end, different representative use- and end of life scenarios need to be defined (NHS 2012) to identify sensitive parameters within the model.

For this purpose, we propose the following approach:

- Development of an average patient (adult or child) and use scenario (if data on user habits are available and the degree of variability regarding the individual treatment is low)
- Development of different scenarios depending on user behavior (if the degrees of freedom within the duration of treatment are high)

The definition of such scenarios, however, depends on numerous parameters, e.g., the API itself and its concentration/DDD, the galenic formulation, the type of disease (acute or chronic), average duration and the way of treatment (self-medication in a household or treatment in a hospital), as well as disposal behavior of the patient (i.e., via domestic waste, take back scheme, sinks/toilets).

Thus, specified rules on a product level are needed to provide modelling guidelines depending on the considered API (see also section 3.4.1).

Some of the required data is already collected by pharmaceutical companies in the form of approval dossiers and business-related data. In addition, publically available information can be utilized, for instance package leaflets, public assessment reports, or publicly available databases by (inter)national institutions and authorities (e.g., DIMDI 2018; DrugBank 2018).

However, regarding the end of life model, only limited data for the behavior of pharmaceuticals in WWTP exist due to the lack of a systematic monitoring (WHO 2012). Emara et al. (2018) (accepted in "Integrated Environmental Assessment and Management") identified some scientific literature which outline the behavior of APIs in WWTP. Additionally, numerous environmental risk assessment (ERA) studies of pharmaceutical substances (e.g., Gilroy et al. 2014; Escher et al. 2011; Celle-Jeanton et al. 2014) exist which provide information on physico-chemical properties and pharmacokinetic characteristics.

Nevertheless, a valid database for APIs containing relevant information on average excretion and metabolization rates as well as potential metabolization products is still missing, and therefore, modelling the use- and end of life phase remains a main challenge within pharma-LCAs.

Due to both the relevance and the complexity of this topic, the development of an appropriate LCI model for the use- and end of life phase of pharmaceuticals needs to be addressed with priority in future research.

3.3.4 Impact assessment

The proposed rules are

- *At least, the following impact categories shall be considered on a product and process level: climate change, human toxicity, ecotoxicity, and resource depletion.*

– **Applicable for:** Pharmaceutical products and processes
– **Specific rules recommended:** No
– **Depends on goal/intended application:** No

- *Pharma-specific impacts shall be considered if an impact assessment model exists. Otherwise, these impacts shall be listed as "additional information."*

– **Applicable for:** Pharmaceutical products
– **Specific rules recommended:** Yes
– **Depends on goal/intended application:** Yes, if the study is intended to compare different products, the pharma-specific impacts should be addressed as "additional information"

The proposed impact categories were identified within existing pharma-LCA studies and further literature (European Union 2010; European Commission 2017). Additionally, a workshop with experts from industry, science, and politics was conducted to identify the most important potential impacts within the sector. Hence, the following impact categories, indicators, and models (Table 3) are determined and shall be applied as a minimum within a pharma-LCA based on this draft PCR:

This choice of impact categories and models is applicable for both pharmaceutical products on a cradle to grave level as well as cradle to gate studies on pharmaceutical manufacturing processes. Additionally, the proposed models are state of the art and already applied in numerous existing LCA studies.

Furthermore, if a cradle to grave analysis on a product level is performed, pharma-specific impacts shall be included due to potential emissions of APIs after excretion into the environment, e.g., endocrine disruption or formation of antibiotic resistance. The selection of impacts depends on the pharmacological subcategory, more specifically the API that is assessed. Therefore, their inclusion is covered in specific rules on the API level.

However, the consideration of potential pharma-specific effects on the environment is still challenging due to the complexity of the physico-chemical reactions, as well as the lack of comprehensive data. Additionally, it is typically assumed in current studies that no API emissions occur during the production processes. Therefore, these impact categories are limited to the use- and end of life phase and thus are not mandatory for LCAs on a process level. This best case assumption, however, depends on the actual practice as well as geographic aspects and should be critically examined (see section 3.4.4).

In current LCA practice, pharma-specific impacts are usually neglected. We propose, however, that these potential impacts shall be generally included, where relevant. However, if the study is intended to compare different products or if proper LCIA methods are not yet available, they should be at least qualitatively reported within the additional information.

3.3.5 Additional information

The proposed rules are

- *The following additional information shall be considered on a product and process level: side effects (e.g., tolerability), multiple pharmacological effects, and pharma-specific impacts (if applicable)*

Table 3 Impact categories and assessment models for pharmaceutical products and processes

Impact category (indicator)	Impact assessment model
Climate change (global warming potential GWP)	▪ IPCC model for Global Warming Potential (GWP) over a 100 year time horizon (IPCC 2013)
Human toxicity (human toxicity potential, cancerogenic/non-cancerogenic)	USEtox model (Rosenbaum et al. 2008, 2011)
Ecotoxicity (freshwater ecotoxicity)	▪ USEtox model (Rosenbaum et al. 2008; Henderson et al. 2011)
Ecotoxicity (marine ecotoxicity, terrestrial ecotoxicity)	▪ USES-LCA 2.0 (Van Zelm et al. 2009)
Abiotic resource consumption (abiotic depletion potential (ADP) fossil and minerals)	▪ Minerals and metals: ADP model (Guinée 1995; Van Oers et al. 2002) (ADP-ultimate reserves) ▪ Energy carriers: ADP model (Guinée 1995; Van Oers et al. 2002) (ADP-fossil)
New pharma-specific impact categories	▪ New characterization models

- **Applicable for:** Pharmaceutical products
- **Specific rules recommended:** No
- **Depends on goal/intended application:** Yes

According to ISO 14025, additional information contains environmentally relevant, product group-specific information which is not part of the life cycle inventory. For this purpose, the following aspects are defined within the draft PCR:

- Side effects: Details on potential adverse effects to the patient and the environment shall be declared based on technical information or leaflets
- Multiple pharmacological effects: Possible multiple pharmacological effects of a pharmaceutical product shall be listed based on every ATC code that is assigned to the API considered in the study
- Pharma-specific impacts: If potential environmental impacts of the pharmaceutical product exist and it is not yet possible to consider these potential impacts within the impact assessment, they shall be qualitatively described

This additional information shall be included if the results are intended to be published. Moreover, further additional information depending on the API under study may need to be investigated. If the study is conducted internally, additional information is optional. In existing pharma-LCAs, however, information on side effects, multiple pharmacological effects, and pharma-specific impacts are completely excluded.

3.4 Cross-cutting issues

The following section provides information on "cross-cutting issues," i.e., interrelated aspects which can have an influence on the environmental performance of pharmaceutical products and thus need to be considered in addition to the therapeutic purpose according to the product subcategory.

3.4.1 Galenic formulation

The galenic formulation is a key parameter for modelling the use phase. Depending on the form of application, different entry pathways to the environment need to be considered. For instance, the API "Ibuprofen" can be applied in various galenic formulations, e.g., as tablet, gel, or suspension. Depending on its form, it is either completely incorporated and excreted afterwards (tablet or suspension) or partly incorporated and partly directly emitted to drain due to wash off (gel). Other pharmaceutical products, e.g., for inhalation purposes, are partly emitted to air due to exhalation while another amount of the API is incorporated.

Furthermore, the galenic formulation also influences the initial dose of the API as well as possible side effects (e.g., tolerability). Thus, the influence of the galenic formulation on the methodological requirements as well as the overall results of the environmental impact assessment should be comprehensively examined.

3.4.2 Type of disease

The type of disease needs to be considered to properly determine the period of application and therefore, the reference flow, within the effect-based functional unit. For this purpose, it is necessary to generally differentiate between acute and chronic diseases. For instance, if the FU refers to a chronic disease, a long-term period of application (e.g., treatment over 10 years) should be applied. However, if the FU refers to an acute disease, a short-term period of application should be used. Moreover, the average likelihood of occurrence (of the disease according to the FU) within this period should be considered if the FU refers to an acute disease and a long-term period of application is used.

Furthermore, the type of disease also influences the generation of potential waste streams during the use phase. For instance, if a chronic disease is considered, it can be assumed that all pharmaceutical products are consumed within the period of application. However, if an acute disease is studied, the potential risk of waste generation due to unused or expired drugs is increasing depending on the packaging size and frequency of the disease within the predefined period.

3.4.3 Pharmaceutical packaging

The packaging of pharmaceutical products is essential to ensure the effectiveness of a medicine. Thus, different complex packaging types exist (e.g., blister, bottles, tubes) which are produced under high hygienic conditions to protect the final product from contamination. Depending on the packaging type and its manufacturing process, potential environmental impacts related to the packaging can change significantly (see Belboom et al. (2011)). In addition, it is necessary to differentiate between packaging for the product itself, i.e., material which has direct contact with the drug ("primary packaging"), packaging without direct contact with the drug, i.e., material that contains one or more packed products ("secondary packaging"), and packaging for the purposes of transport, handling, and/or distribution ("tertiary packaging"). Based on this distinction, different end of life scenarios shall be specified for the LCA study. For instance, secondary and tertiary packaging should be assumed to be recycled while primary packaging should be incinerated due to the contamination with the API. Therefore, the composition and manufacturing of the pharmaceutical packaging can be a critical issue with

regard to the potential environmental performance of a pharmaceutical product and thus shall be included and clearly addressed in future studies.

3.4.4 Geographic aspects

Spatial characteristics of the pharmaceutical sector need to be considered if the geographic scope of the PCR is defined. As described in the section 3.3.4, we assume that no API emissions occur during the production processes by limiting the application of pharma-specific impacts to the use- and end of life phase. However, this assumption may be applicable for developed countries but do not reflect the factual situation in other API-producing countries such as Bangladesh, India, China, and Pakistan. Rehman et al. (2015) describe that most of the pharmaceutical manufacturing sites in these countries are not compliant with local environmental legislation. Therefore, the direct discharge of contaminated process wastewater into the environment or domestic sewer systems poses an enormous risk for an uncontrolled release of APIs in the environment.

The geographic scope of the PCR should take such geographic differences and characteristics into account.

In addition, it should be generally determined in a proper way to ensure the technical and spatial representativeness of the process models (e.g., default scenarios regarding the distribution, use- and end of life phase) as well as the data that is utilized (e.g., regarding wastewater treatment technology or power generation). Thus, the definition of the PCRs geographic validity is crucial for modeling the product system.

4 Conclusions

The lack of harmonized rules for LCA studies in the pharmaceutical sector leads to several methodological differences and shortcomings in existing pharma-LCAs, e.g., use of mass-based functional units without reference to the pharmacological function of the product, general exclusion of the use- and end of life phase, and the lack of characterization models to include pharma-specific impacts which can lead to incomplete or even misleading results. Therefore, existing studies are barely comparable.

To overcome these obstacles, we propose a draft PCR for pharmaceutical products and processes. Within the draft PCR, the general structure, the granularity, i.e., the level of detail of the product category, as well as methodological requirements for pharmaceutical products and processes are determined and discussed with regard to their applicability and the current practice in existing pharma-LCAs. The methodological requirements usually depend on the product system as well as the goal and intended application of the study. In addition, some rules need to be specified depending on the considered API within predefined subcategories. Moreover, cross-cutting issues, i.e., galenic formulation, type of disease, pharmaceutical packaging and geographic aspects, and their influence on the methodological requirements within the draft PCR, are identified and discussed.

The system boundaries of future pharma-LCAs shall be defined with regard to the product system and the intended application. In addition, two different functional units, namely mass-related and effect-related, shall be applied depending on the product system which is assessed. The use- and end of life phase is mainly based on numerous assumptions. However, these life cycle stages shall be included if an LCA study on a product level is performed. Nevertheless, existing LCA studies exclude these downstream processes and therefore fail to include pharma-specific emission pathways and impacts. Furthermore, additional information, i.e., information on side effects, multiple pharmacological functions, as well as pharma-specific impacts that are not part of the environmental impact assessment shall be at least qualitatively described if the study is intended to be published.

5 Outlook

This work emphasizes the need for harmonized rules to conduct future LCA studies in the pharmaceutical sector. Furthermore, it revealed some remaining challenges. Thus, future work should focus on modelling the use- and end of life phase, developing characterization models to assess pharma-specific impacts, and defining appropriate indicators to include pharma-specific additional environmental information on a quantitative level.

This draft PCR is currently tested and refined by several case studies with partners from industry and science to ensure its applicability.

The presented draft PCR is only valid for pharmaceutical products for human use as well as their manufacturing processes. Veterinary medicine, cosmetics, or basic chemicals are not within the scope of this work, but future work could expand the scope to cover these important sectors as well.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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3.2 Addressing the use and EoL of pharmaceutical products in LCA

This chapter contains the following publication:

- Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment**. Int J Life Cycle Assess **25**, 1436-1454 (2020). https://doi.org/10.1007/s11367-019-01722-7

In this publication, a major gap in existing LCAs from the pharmaceutical sector is addressed, namely the inclusion of the use and EoL stage. Since the majority of pharmaceutical emissions are assumed to occur in these life cycle stages due to excretion or disposal of unused medicine, their consideration is particularly important if pharmaceuticals are assessed which are expected to have a significant impact after their release to the environment. To this end, a model for the use and EoL stage is developed to quantify potential API emissions arising from these life cycle stages (objective O.2.3). Since the model depends on some regional assumptions (e.g. regarding waste water treatment technology), we chose Germany as geographic scope but indicated if the model may need to be modified in case of other regions are being assessed. To increase the applicability of the model and incorporate different potential emission pathways of an API, we differentiate between three main galenic formulations: (1) Pharmaceuticals for oral, other mucosal or parenteral applications; (2) Pharmaceuticals for cutaneous application; (3) Pharmaceuticals for pulmonary application. Depending on their form of application, the use and EoL stage is qualitatively described and associated flows of the API are identified. Based on the procedure to calculate the predicted environmental concentration (PEC) of an API in surface water by the European Medicines Agency (EMA) (EMA 2018), different approaches are then developed to quantify these API flows for each galenic formulation.

The use stage comprises the application and storage of the pharmaceutical product, the disposal of packaging and unused medicine, as well as the pharmacological behavior of the API in the body. After excretion, exhalation or wash off, the API and its metabolites enter the EoL stage. Here, it is either directly emitted to air (after exhalation) or to the waste water treatment plant (WWTP) (after excretion or wash off). In the WWTP, the API and metabolites are (partially) removed and residues enter the surface water bodies. The removal rate and distribution behavior of the substances to air, sewage sludge or effluent during the WWT are estimated with the tool SimpleTreat 4.0 by the Dutch National Institute for Public Health and the Environment (RIVM).

The feasibility of the model is finally tested for the oral intake of ibuprofen. Here, we are able to quantify all flows related to the API (parental compound) with publicly available data even though the quality and magnitude of some parameters (such as the biodegradation rate) vary significantly. The metabolites are excluded since this calculation only serves as a proof of concept.

The supplementary material to this publication is presented in Appendix A. 2. Supplementary material to publication 2. It comprises the following information:

- Input parameters (‘base-set data’) for the calculation with SimpleTreat 4.0

Due to an error during typesetting, a correction article was published. It is attached to the original publication in this section.

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HEALTHCARE

Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment

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Abstract

Purpose Pharmaceutical residues in the environment can pose significant risks to ecosystems and human beings due to adverse pharma-specific effects. Existing life cycle assessment (LCA) studies do not usually consider the use and end-of-life (EoL) phase of pharmaceuticals and thus exclude relevant potentially toxic emissions of an active pharmaceutical ingredient (API). Therefore, a simplified inventory model for the use and EoL phase of pharmaceuticals is provided by estimating API flows and emissions to the environment.

Methods Both the qualitative description of the use and EoL phase of pharmaceuticals and the quantification of the flows within each life cycle phase are based on literature and expert knowledge. Existing approaches to determine the API emissions are adjusted to make them applicable in LCA. In addition, different uses and EoL scenarios (e.g. depending on the patients' disposal behaviour) are specified, and assumptions are highlighted. Finally, the model is exemplarily applied to the oral intake of ibuprofen to test its applicability.

Results and discussion Eleven potential flows and emissions of an API are identified and quantified for different application forms (pulmonary, oral, cutaneous). The model is applied to ibuprofen where potential API emissions result from administered and unused products. Referred to the administered amount of ibuprofen (reference flow), the product is mainly metabolized (73.1%). The unmetabolized (parental) compound enters the sewage treatment plant where it is degraded (13.94%), or emitted to surface water (8.35%), air (0%) and sewage sludge (0.36%). The remainder cannot be clearly assigned to one of the flows (4.25%). The results of this example are hardly comparable to existing measured data because they are related to the functional unit. The effect of assumptions, limitations due to data availability and the geographic scope reveal the need for further research.

Conclusions To facilitate the consideration of the use and EoL phase of pharmaceuticals in future pharma-LCAs, a simplified inventory model specified for German conditions, is provided which allows to calculate inventory results with easily and publically accessible data. However, remaining challenges such as the lack of data to model the behaviour of metabolites in the sewage treatment plant, missing approaches to include specific pharmaceuticals (e.g. hormones, anticancer drugs), the consideration of other sewage treatment technologies such as ozonization, the integration of API emissions from sewage sludge (e.g. due to the use as fertilizer) or the scope expansion with regard to the geographic validity of the model shall be further examined.

Keywords Inventory • Life cycle assessment • End-of-life • Pharmaceuticals • Product category rules • Use

1 Introduction

Several studies discuss pharmaceutical emissions to different environmental compartments and their potential adverse effects on certain organisms (e.g. Aguirre-Martínez et al. 2015; Al Aukidy et al. 2012; Brandt et al. 2015; Celle-Jeanton et al. 2014; Gilroy et al. 2014; Gómez-Canela et al. 2016; Östman et al. 2017; Petrie et al. 2015). To integrate these impacts into the environmental assessment of pharmaceutical products, a consideration of the whole life cycle, from

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resource extraction and production of basic chemicals, manufacturing of the active pharmaceutical ingredient (API), galenic formulation and packaging, to the distribution, use and end-of-life (EoL) (excretion and/or disposal of the product) is indispensable.

1.1 Pharma-specific emissions in life cycle assessment

The number of life cycle assessment (LCA) studies in the pharmaceutical sector is very limited and additionally, existing LCA studies of pharmaceuticals (hereinafter referred to as 'pharma-LCAs') usually focus on the (in-) direct emissions caused by pharmaceutical production processes (e.g. due to energy use or application of solvents) from a cradle-to-gate-perspective. As a result, the largest flow of pharmaceutical emissions i.e. the release of an active pharmaceutical ingredient (API) (as parental compound or metabolite) into the environment, occurring from excretion after application of a pharmaceutical, and the associated potential ecotoxicological effects from the use and EoL are usually excluded. While first conceptual ideas to include these life cycle stages in future pharma-LCA studies are presented in a previous publication (Siegert et al. 2018), to the best of our knowledge, a specific, comprehensive model to quantify and include API emissions occurring from the use and EoL phase in LCA does not exist yet (Emara et al. 2018).

In general, pharmaceutical emissions can be measured to obtain Measured Environmental Concentrations (MECs). Even though numerous studies have been published in the past that describe the occurrence of pharmaceuticals in natural compartments (such as groundwater, surface water and soils), there is a lack of systematic and exhaustive monitoring of pharmaceutical substances in the environment (Arnold et al. 2014). Furthermore, analytical methods are usually time consuming and very expensive (Alder et al. 2010). Alternatively, many publications estimate pharmaceutical emissions based on models to determine Predicted Environmental Concentrations (PECs) (see chapter 2.2).

However, these approaches reveal several shortcomings from an LCA perspective:

First, the models usually do not include all potential API-specific mass flows i.e. API flows within the technosphere (hereinafter called 'API flows') and API-specific elementary flows i.e. API flows between technosphere and ecosphere (hereinafter called 'API emissions'). For instance, emissions due to the disposal of unused products or other emission pathways than excretion via faeces or urine (such as exhalation or bathing after dermal use) based on different galenic formulations/forms of application are mostly not considered. As a result, some API emissions (e.g. from exhalation) are ignored and the amount of API entering the different environmental compounds (soil, air, water) is probably neglected or underestimated (Kostich and Lazorchak 2008). Hence, these API emissions need to be included to enable a complete and comprehensive assessment of the potential environmental impacts (Daughton and Ruhoy 2009).

Second, PEC values are usually calculated as part of environmental risk assessment (ERA) studies which represent predicted concentrations in the natural environment. However, calculations based on concentrations (e.g. mg L^{-1}) are not practicable due to the relative character of LCA where potential environmental impacts are assessed based on absolute values (e.g. in kg or kWh) and referred to the functional unit (FU) (ISO 2006a; Klöpffer and Grahl 2009).

1.2 Goal and scope

The goal of this paper is to develop an applicable yet comprehensive life cycle inventory model to consider API emissions in the use and EoL phase of pharmaceutical products. This model is an integral part of draft product category rules (PCR) for the pharmaceutical sector. Hence, this paper can be seen as complementary to the previous publication on harmonized rules for future LCAs on pharmaceutical products and processes (Siegert et al. 2018).

For this purpose, we (1) define and qualitatively describe the use and EoL of a pharmaceutical (see chapters 2.1 and 3.1), (2) develop a new model for the application in LCA based on existing approaches to quantify all potential API flows and emissions to the environment during the use and EoL phase (see chapters 2.2 and 3.2) and (3) present a proof of concept by applying the model to the exemplary case of a highly relevant pharmaceutical, namely ibuprofen (see chapters 2.3 and 3.3).

Furthermore, geographic characteristics and assumptions (e.g. state of the art of waste water treatment) need to be considered and fixed for the new model. While the basic principles of the approach are widely applicable, we specify it here for Germany as geographic scope.

Finally, the model only includes inventory flows of the API under study i.e. mass-based inputs and outputs. The impact assessment of these flows follows the usual LCIA procedure according to ISO 14044 (2006b), chapters 4.4.2 and 4.4.3, and is not further detailed in this publication. The focus of this paper is the API emissions. Other emissions from processes within the use and EoL phase such as greenhouse gas emissions resulting from the treatment of secondary packaging shall also be included in future pharma-LCAs. However, contrary to the API emissions, these aspects are already well studied and included in many other studies within (e.g. Belboom et al. 2011; Raju et al., 2016) and outside the pharmaceutical sector (e.g. Razza et al. 2015; Zampori and Dotelli 2014).

2 Methods

In the following chapters, we first outline the procedure to define and qualitatively describe the use and EoL phase of pharmaceuticals (see chapter 2.1). In chapter 2.2, we present

a basic approach commonly applied in risk assessment for the quantification of API emissions occurring from the use of pharmaceuticals based on which the use and EoL model is later developed. Finally, we describe the application of the model to the case of ibuprofen (see chapter 2.3). As the main outcome of this study, the final model is presented in the results section (see chapter 3.2).

2.1 Definition of the use and EoL phase of pharmaceuticals

The use phase can be described as the expected use of a product by the end user including all activities and products that are necessary to provide the function of the product. The use phase starts with the use of the product and ends with entering the EoL phase including all necessary transport. The EoL phase covers the transport and treatment of products after use and waste products as well as primary packaging (European Commission 2018).

Based on this general definition, the qualitative description of the use and EoL phase of pharmaceuticals and delimitation to other life cycle phases was conducted. By using existing literature as well as expert knowledge from the pharmaceutical sector, all processes and flows that are related to the application of pharmaceutical products were identified e.g. API emitted to raw sewage and its removal in the sewage treatment plant (STP). For this purpose, semi-annual meetings with a panel consisting of eight professionals from science, industry and politics as well as non-governmental organizations with expertise in pharmacology and pharmacokinetics, pharmaceutical technology, good manufacturing practices, compliance and toxicology were conducted. To address specific issues, individual personal consultations with these and other additional experts from various fields e.g. environmental management in hospitals, waste management and waste water treatment were performed.

In addition, interdependencies between processes and flows as well as potential API emissions to the environment (e.g. to air due to exhalation) were illustrated in a system diagram (see Fig. 1).

This qualitative description of the use and EoL phase depends on several assumptions as well as the geographic scope of the model. For instance, the API can either enter the environment via raw sewage that is released untreated in some countries, or via effluent after being partly removed in a STP (Kookana et al. 2014). Thus, country-/region-specific conditions according to the geographic scope (see chapter 1.2) are considered.

2.2 Development of the life cycle inventory model

To develop a comprehensive yet simplified and easy to use life cycle inventory (LCI) model that enables to quantify each flow within the use and EoL phase, the following steps were performed:

First, a non-comprehensive literature screening was performed to identify existing approaches that can serve as a conceptual basis for the use and EoL model to be developed in this study (e.g. Besse et al. 2012; Chèvre et al. 2013; Christensen 1998; Han et al., 2014; Han and Lee 2017; Johnson and Williams 2004; Jones et al. 2002; Khan and Ongerth 2004; Landry and Boyer 2016; Ong et al. 2018; Ortiz de García et al. 2013; Perazzolo et al. 2010; Pereira et al. 2017; Winker et al. 2008). The screening was conducted without time restriction regarding the publication date by using Google scholar with combined keywords such as 'pharmaceuticals', 'pharmacokinetics', 'emission', 'occurrence', 'fate', 'distribution', 'model', 'life cycle' and 'waste water'. Since we focused on identifying existing modelling approaches to estimate the different API emissions and flows during the use and EoL of pharmaceuticals, analytical studies with the sole purpose to present measured concentrations of APIs in the environment were excluded. In addition, only few ERA studies were considered because they usually apply identical calculation rules to determine PEC values. Special attention was given to approaches to model the pharmacokinetic behaviour of an API in the body. This first screening provided not only guidance how API flows and emissions can be modelled, but also identified supportive data sources to quantify the model parameters. Furthermore, this generic literature was complemented by the few existing LCA studies that take API emissions into account. These studies were identified and reviewed by Emara et al. (2018).

The procedure to calculate the predicted environmental concentration of an API in surface water according to phase II Tier B ('Environmental fate and effects analysis') described within the 'Guideline on the environmental risk assessment of medicinal products for human use-draft' (revised version 1.0) published by the European Medicines Agency (EMA 2018) was identified as a suitable starting point for further model development since it is already incorporated in European healthcare regulations and hence, widely accepted in the sector. Unlike the phase I risk assessment, the second phase includes the metabolization (i.e. excretion rates) of the API and was therefore applied to consider metabolization as one major factor that affects the emission of an API to the environment (Besse et al. 2008). The calculation includes several aspects that are necessary to determine the emission of the API to water bodies (e.g. dosage, excretion rate and capacity of the local STP):

$$\mathrm{PEC}_{\mathrm{SURFACEWATER}} = \frac{(\mathrm{DOSE}_{\mathrm{AS}} \times F_{PEN} \times F_{\mathrm{EXCRETA}})}{(\mathrm{WASTEW}_{\mathrm{INHAB}} * \mathrm{DILUTION})} \quad (1)$$

where $\mathrm{DOSE}_{\mathrm{AS}}$ [mg inh^{-1} day^{-1}] describes the maximum daily dose of the active substance (AS) consumed per inhabitant,

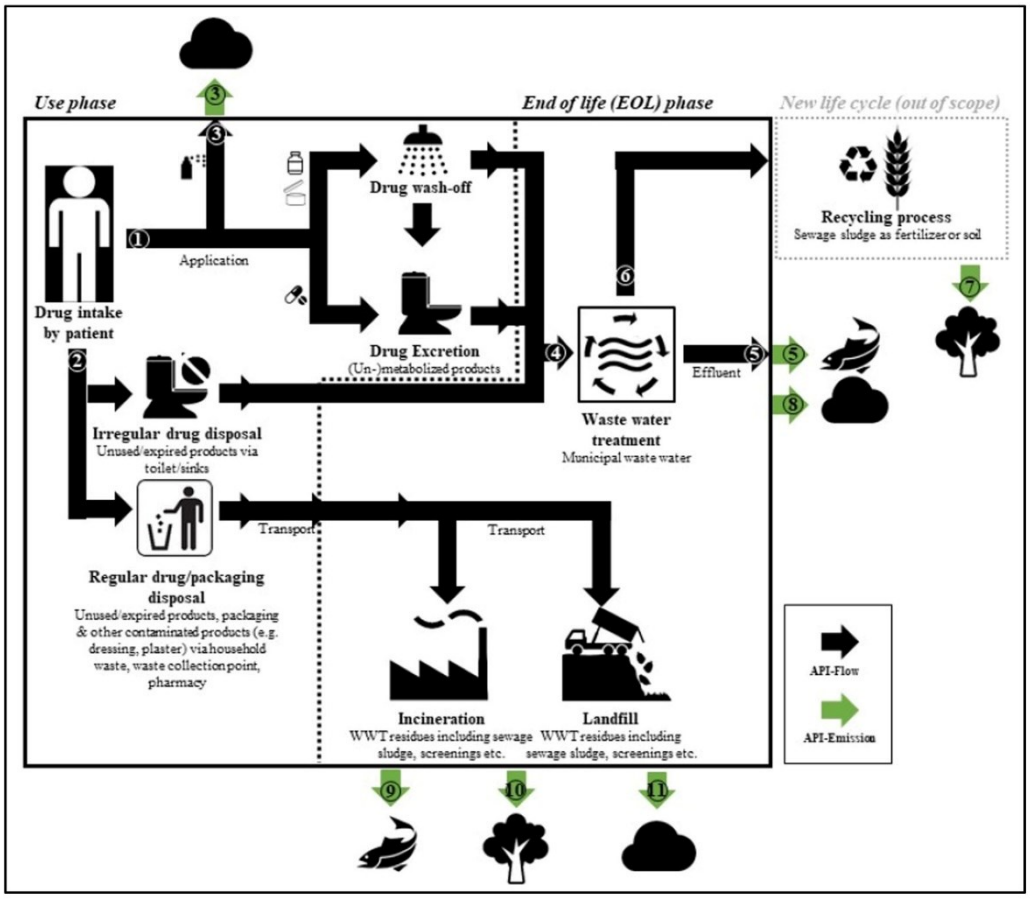

Fig. 1 System diagram to illustrate the use and EoL phase of a pharmaceutical product The qualitative model contains all API flows (# 1–6) and emissions (# 3, 5, 7–11) that can occur during the use and EoL of pharmaceuticals

F_{PEN} [−] the fraction of population receiving the active substance during a given time, $F_{EXCRETA}$ describes the excretion rate [−], $WASTEW_{INHAB}$ [L inh^{-1} day^{-1}] describes the amount of wastewater per inhabitant and day and the DILUTION [−] factor which considers the dilution of the substance after entering the surface water (EMA 2018).

Second, this source-based approach used in ERA was adjusted to enable the application in LCA:

- The $PEC_{SURFACEWATER}$ describes a predicted concentration in water bodies due to excretion. However, all results shall be provided as mass flows to make them applicable in LCA i.e. concentrations need to be converted to absolute mass flows which are referred to the FU (see also chapter 1.1). Therefore, the predicted environmental concentration in [mg L^{-1}] was replaced by the mass of an API emission to air or surface water (API per functional unit) e.g. in [mg].

  Furthermore, the EoL of unused pharmaceuticals, other emission pathways such as exhalation or additional emissions to sewer due to wash off and the excretion of metabolites are not considered in Eq. (1). These potential API flows were added in our model. For this purpose, the excretion rate $F_{EXCRETA}$ was either adopted, or replaced by introducing other pharmacokinetic parameters such as the absorption and metabolization rate since $F_{EXCRETA}$ only reflects the amount of an API that is excreted in the parental form after oral application.
- $WASTEW_{INHAB}$ (amount of waste water per inhabitant) and F_{PEN} (market penetration) are negligible because they refer to a total amount of pharmaceutical consumption by the population of a certain country. However, in LCA, all in and outputs are referred to the FU. Thus, a determination of the total amount of consumed or prescribed pharmaceuticals for a whole population to calculate the PEC is not necessary for the application in LCA. The FU and the corresponding reference flow i.e. the amount of a specific pharmaceutical product to treat a disease over a predefined treatment period (TP) depend on the goal and scope of a study and are individually specified by the developer of a study for each LCA.

- The DILUTION factor refers to the amount of API that already entered the environment/surface water. It is usually considered in existing impact assessment models (e.g. USEtox) and, therefore, not part of the inventory.
- Terms that describe the behaviour of an API in the STP, such as treatment efficiency (i.e. degradation rate) and the distribution of the pharmaceutical compound to sewage sludge, effluent and evaporation, to air are not yet included in Eq. (1) and were added.

In addition to these adjustments, different scenarios depending on the application form and patients' disposal behaviour were defined and delineated. All specific assumptions are additionally summarized at the end of each chapter.

2.3 Application of the model

The model was exemplarily tested for the pharmaceutical product ibuprofen. Table 1 provides an overview on parameters that are used for this example:

Ibuprofen was selected because it is a highly ranked pharmaceutical according to the priority list by Voogt et al. (2009) where different aspects such as consumption, toxicity and persistence are evaluated. As potential data sources, not only experimental/analytical data from literature or data bases (e.g. for excretion rates, removal rates) but also estimation tools or values based on expert knowledge (see chapter 2.1) were utilized. The results are presented in chapter 3.3. The purpose of this example was to illustrate the application of the modelling approach and to identify potential challenges. A detailed LCA study of ibuprofen, its different galenic formulations and metabolites was beyond the scope of this work.

3 Results

In this section, first, a general qualitative description of the use and EoL phase of a pharmaceutical product with regard to the geographic scope is presented. In addition, all potential API flows and emissions to the environment are identified (see chapter 3.1). Second, approaches to calculate the API flows and emissions depending on the form of application are described for the chosen geographic scope (see chapter 3.2). Here, the results of the process steps described in chapter 2.2 are combined and described together (chapters 3.2.1 and 3.2.2), whereby the results from the model application on ibuprofen are presented separately in chapter 3.3.

3.1 Use and EoL phase of pharmaceuticals—a qualitative description

The use phase encompasses the intake and storage of a pharmaceutical product as well as the use of additional devices (e.g. inhalers) if these are necessary for the application of the API. Furthermore, it includes the pharmacological behaviour of the API in the body i.e. the liberation, absorption and distribution ('invasion') as well as the metabolization and excretion ('elimination') (Efferth 2006; Langner et al. 2011). After use, the API enters the EoL phase by either being excreted or washed off and entering the STP afterwards, or it reaches the environment as elementary flow via exhalation. Unused/expired products as well as primary packaging (i.e. material that contains the product and has direct contact with the final preparation e.g. blister) and secondary packaging (i.e. material that contains one or more product(s) and no direct contact with the preparation e.g. folding carton) leave the use phase through disposal and enter the EoL phase directly without change of their inherent product characteristics. Here, we distinguish between regular (e.g. via residual and/or commercial waste) and irregular (e.g. via sinks and toilets) disposals of unused pharmaceuticals. These processes and flows are also described by existing studies (Daughton and Ruhoy 2009; Ebele et al. 2017; Han et al., 2014; Heberer 2002; ISOE 2008; Li 2014; Mompelat et al. 2009; Monteiro and Boxall 2010; WHO 2011; NHS 2012, 2012; EMA 2006; Caldwell 2016). The following sections qualitatively describe the intake and behaviour of pharmaceuticals in the human body as well as the EoL of used and unused pharmaceuticals:

Table 1 Relevant parameters for the use and EoL phase specified for the example of Ibuprofen

Parameter	Example
FU	Treatment of an inflammation of an adult in Germany over 1 week
Application form	Coated ibuprofen tablets
API concentration	400 mg
Classification according to the 'Anatomic Therapeutic Chemical' (ATC) classification system	M01AE01 (DIMDI 2019)
Defined daily dose (DDD)	1200 mg/day (oral) (DIMDI 2019)
Place of treatment	At home

3.1.1 Intake and behaviour of pharmaceuticals in the human body

In general, pharmaceuticals can be either used at home or in a healthcare facility (i.e. hospital or nursing home) whereby the point of drug administration can differ from the 'point of emission (PoE)' (e.g. in case of outpatient treatment). A direct application in medical practices is not considered in the model due to German legislation ('dispensing ban') i.e. doctors are not allowed to commercially supply patients with pharmaceutical products (BPB 2012).

The effect of the human organism on the pharmaceutical product after its application is called 'pharmacokinetics' and depends on various parameters (e.g. route of application, state of health, food intake or chemical and physical characteristics of the API). If the API is absorbed, it enters the bloodstream and is distributed in the body. After intake, the API can be either excreted as parental compound or as metabolite formed by metabolization processes. Excretion and metabolization/biotransformation processes are summarized as 'elimination'. Most of the pharmaceuticals are excreted with urine, but partly also via faeces, sweat, exhalation, saliva and breast milk (Aktories and Forth 2013). Whereas the excretion via sweat, saliva or pancreas secretion are assumed to be negligible for the elimination of the API, the excretion via breast milk can be relevant from a pharmacological point of view (Langner et al. 2011).

3.1.2 EoL of used and unused pharmaceuticals

After use, the API is excreted or washed off and enters the sewer system and STP where it is partially removed (Jelic et al. 2011). The same applies for the unused fraction of pharmaceuticals that is disposed irregularly via toilets or sinks. Since we chose Germany as the geographic scope, it is assumed that the PoE is connected to a STP. This assumption is valid for the majority (> 95%) of the German population. Almost all of the existing STP work with (minimum) three treatment stages: mechanical pre-treatment, biological stage and additional purification with nutrient elimination (BMU, 2019). A pre-treatment of wastewater from healthcare facilities (e.g. hospitals) or separate urine collection would be a promising way to decrease the amount of API that enters the STP influent. However, this is not considered in the model because it is not current practice in Germany (VDI 2015). Depending on the chemical and physical properties, the API can be either degraded, or persist in the effluent of the STP, evaporate or accumulate in solid matter and are removed as sewage sludge (Struijs 2014). Hence, API residues can enter the environment if it evaporates, the effluent is discharged to surface water or if sewage sludge leaves the current product system and is used in a new one e.g. utilization as fertilizer. Thus, the behaviour of an API in the sewage sludge during and after processing and the potential API emissions to soil after land application are part of a new product system and therefore, outside the scope of this publication.

If pharmaceuticals in households remain unused, these products (including primary and secondary packaging) as well as primary packaging from used pharmaceuticals are usually disposed as residual waste, at local waste collection points or single pharmacies (DECHEMA 2019), whereas a systematic take-back scheme for expired/unused pharmaceuticals does not exist (DUH 2013). This waste is then usually incinerated or further processed in a mechanical-biological treatment plant and partly landfilled. In healthcare facilities, unused pharmaceuticals are disposed as non-hazardous commercial waste and incinerated in a combustion plant (Voigt 2018).

The use and EoL phase including API flows and emissions to water bodies, air and soil (circled numbers 1–11) are illustrated in Fig. 1. API emissions to soil occurring from land applications of sewage sludge (#7) are not further considered for the quantitative model as they are part of a new product system:

Table 2 summarizes all flows that are illustrated in Fig. 1 and qualitatively described in the previous sections:

For the model, the API flows and emissions listed in Table 2 are quantified and further explained in the following chapter 3.2.

3.2 Model

This chapter includes the generic modelling approach as well as relevant assumptions and simplifications. First, some assumptions and limitations valid for both: the use and EoL phase are made to simplify the processes in reality and thus facilitate the model development and its application in an LCA context:

- We do not differentiate between genders and the different members of population (male, female, pregnant females, menstrual females, menopausal females, females taking hormone replacement therapy (HRT)) due to the lack of available pharmacokinetic data.

- Furthermore, the model only differentiates between children and adults in terms of determining the DDD (according to the ATC classification scheme or leaflet) if the FU and the reference flow are defined. This differentiation only applies if different DDD for adults and children are provided based on e.g. age, bodyweight and body surface (WidO 2018).

- The influence of diseases (e.g. renal insufficiency), other pharmaceuticals and ingestion of food on the pharmacokinetic behaviour of the pharmaceutical product intended to be assessed are not reflected because these aspects are

Table 2 API flows and emissions in the use and EoL phase of pharmaceuticals

Flow # (see Fig. 1)	API flow/emission	Description	Life cycle phase
1	API_{Admin}	API (parental compound only) that is actually consumed by the patient	Use phase
2	API_{Unused}	API (parental compound only) contained in the pharmaceutical product that is unused (e.g. due to expiration) to regular/irregular disposal	Use and EoL phase
3	$API_{Exhaled}$	API (parental compound and metabolites) that is directly emitted to air as an elementary flow due to exhalation	Use phase (elementary flow)
4	$API_{Influent}$	API (parental compound and metabolites) in waste water stream (due to excretion, wash off or irregular disposal) that enters the STP	Use and EoL phase
5	$API_{Effluent}$	API (parental compound and metabolites) in STP effluent (after removal) to surface water	EoL phase (elementary flow)
6	$API_{Solid\ matter}$	API (parental compound and metabolites) that accumulate in solid matter and is removed afterwards as sewage sludge	EoL phase
7	$API_{Fertilizer}$	API (parental compound and metabolites) contained in fertilizer produced from sewage sludge	New life cycle (out of scope)
8	$API_{Evaporated}$	API (parental compound and metabolites) that evaporates during waste water treatment	EoL phase (elementary flow)
9	$API_{Waste\ disposal\_water}$	API (parental compound only) emitted to water due do waste disposal activities (incineration and/or landfill)	EoL phase (elementary flow)
10	$API_{Waste\ disposal\_soil}$	API (parental compound only) emitted to soil due do waste disposal activities (incineration and/or landfill)	EoL phase (elementary flow)
11	$API_{Waste\ disposal\_air}$	API (parental compound only) emitted to air due do waste disposal activities (incineration and/or landfill)	EoL phase (elementary flow)

individual and very uncertain to estimate. Hence, the model underlies 'ideal scenarios' i.e. the human being is regarded as a black box and publically available pharmacokinetic data is used.

- We only differentiate between parental compound and metabolite. Other transformation products formed outside the body by solar radiation, bacteria or technically by treatment processes within the STP (Kümmerer et al. 2011) are not considered due to the lack of data for these reactions.
- The excretion via sweat, pancreas secretion or saliva are not considered due to the low percentage of the overall excretion and the lack of publically available data. The excretion via breast milk is not considered in the model due to the fact, that, after intake and elimination, urine and faeces of infants are usually excreted to diaper, disposed via residual waste and incinerated. Thus, it is assumed that no API emissions to the environment occurs in this case.

Further assumptions and simplifications that are specific for the use and EoL phase are described and in the following chapters.

3.2.1 Use phase

In the following, the modelling approaches for all related API flows and emissions as well as specific assumptions made for the use phase are presented. Here, we differentiate between the determination of used and unused products, and the behaviour in the human body depending on the form of application.

Determination of used and unused products It is necessary to differentiate between the amount of API that is actually used within the TP (API_{Admin}, in mg) and leftovers which are not used or expired (API_{Unused}, in mg), and to determine these two API flows.

The amount of pharmaceuticals that is administered depends on the scope of the study, particularly on the definition of the FU and the reference flow defined for the LCA study.

The FU is defined as the 'treatment of [one or more] [child(ren) or adult(s)] in [geographic region] with [disease/indication] for [period of application]'. The reference flow is the required DDD (in mg day^{-1}) packed and ready for intake, multiplied with the TP (in d) i.e. the amount of API that is needed to fulfil the therapeutic purpose over the predefined period and, if needed, additional medical devices to administer the drug or additional pharmaceutical products to guarantee the therapeutic effect ('combination preparation') (Siegert et al. 2018).

Based on this, API_{Admin} (see flow 1 according to Table 2) equals the reference flow defined for the LCA case study and can be determined with Eq. (2):

$$API_{Admin} = \text{Reference flow} = DDD \times TP \quad (2)$$

The amount of unused products (see Eq. (3)) i.e. the waste of products containing API_{unused} (flow 2 according to Table 2) (also called 'loss rates at consumer' according to European Commission (2018)) can be either determined based on specific information on the loss rates or set as a default value. The default value can be defined as a percentage of the administered API that is not applied and hence directly enters the EoL phase. As there is no statistical data on unused pharmaceuticals in Germany, we propose to follow the PEF recommendations provided by the European Commission (2018) for default loss rates at consumer for healthcare products:

$$API_{Unused} = \text{Reference flow} \times \text{loss rate} \quad (3)$$

Product waste is disposed regular or irregular without changes of the pharmacological properties of the product. However, patient behaviour regarding the disposal of pharmaceuticals is very individual (Götz and Keil 2007; Martin et al. 2005) and reliable statistics do not exist. Therefore, the following default disposal rates based on Bartsch (2010) are used for the model which depend on the physical state of the product:

- Solid products: 85% regular, 15% irregular
- Liquid products: 55% regular, 45% irregular
- Average: 70% regular, 30% irregular

Based on these disposal rates, Eqs. (4) and (5) are applied to determine the regular and irregular disposed amount of unused pharmaceuticals:

$$API_{\text{Regular disposal}} = API_{Unused} \times \text{Disposal rate}_{Regular} \quad (4)$$

$$API_{\text{Irregular disposal}} = API_{Unused} \times \text{Disposal rate}_{Irregular} \quad (5)$$

After disposal, the unused products enter the EoL phase (see chapter 3.2.2).

Specific assumptions:

- If a product is disposed irregularly, it is assumed that 100% of the API (parental compound) enters the sewer system.
- The irregular drug disposal by patients in healthcare facilities is expected to be negligible because daily dosages are usually provided by the staff or hospital pharmacy and individually prepared for each patient on the ward (BVL 2018).

Fate in the human body The fate of an API in the human body after its administration (API_{Admin}) differs depending on the application form. To calculate the respective API flow that is excreted to waste water and subsequently enters the STP ($API_{Influent}$, see flow 4 according to Table 2), we distinguish between pharmaceuticals for (1) oral, other mucosal or parenteral applications, (2) cutaneous application and (3) pulmonary application.

1. Pharmaceuticals for oral, other mucosal or parenteral applications with/without absorption:

Here, the API is either absorbed through mucous membranes (e.g. oral, rectal, nasal), conjunctiva and injections (e.g. tablets, eye drops), and excreted afterwards as parental compound (API_{abs_par})/metabolized product (API_{abs_met}), or the API is not absorbed and excreted as parental compound (API_{nabs_par}). Specific cases are parenteral applications i.e. intravenous, intra-arterial, or intracardiac administrations, where the API directly enters the blood and lymphatic vessels. Thus, the API can be (partly) metabolized, by-passing the absorption process.

For our model, we consider both absorbed and unabsorbed fractions of an API by following the approach of Ortiz de García et al. (2013). For this purpose, pharmacokinetic properties of the API under study i.e. excretion rate for parental compound, API-specific absorption rate A (in %) and substance-specific metabolization rate M_i (in %) are used to calculate the excreted fraction to waste water (Eqs. (6), (7) to (8)):

$$API_{abs\_par,\ excreted} = \text{Excretion rate}_{par} \times DDD^{*}TP \times A \quad (6)$$

$$API_{abs\_met\ i,\ excreted} = DDD \times TP \times A \times M_i \quad (7)$$

$$API_{nabs\_par,\ excreted} = DDD \times TP \times (1-A) \quad (8)$$

The overall amount of $API_{Influent}$ consists of parental compounds of the API and metabolites, which shall be calculated separately. When calculating $API_{Influent}$ for parental compounds, the unused and irregular disposed fractions of the pharmaceutical product need to be added to the excreted fraction (Eq. (9)). For each metabolite *i*, the amount of $API_{Influent}$ corresponds to the absorbed, metabolized and excreted fractions (Eq. (10)):

$$API_{Influent}\,(\text{parental compound}) = API_{\text{Irregular disposal}} + API_{abs\_par,excreted} + API_{nabs\_par,excreted} \quad (9)$$

$$API_{Influent}(\text{metabolite } i) = API_{abs\_met\ i,excreted} \quad (10)$$

After excretion, the total amount of (parental) API and its metabolites leaves the use phase and enter the EoL phase as STP influent.

Specific assumptions:

- Due to the principle of mass balance, a further differentiation between application forms is not necessary. The amount of API that is administered correspond to the API that is eliminated and excreted afterwards

- Accumulation in the body (e.g. in fatty tissue) is only relevant if temporal aspects are considered. However, LCA assesses a steady state. As a result, it is assumed that the amount of accumulated API is included in $API_{Influent}$ for parental compounds as well as metabolites
- We do not differentiate between free and conjugated metabolites

2. Pharmaceuticals for cutaneous application with/without absorption:

If pharmaceuticals for cutaneous application (e.g. ointments, cremes, gels) are used, they are partly absorbed and excreted afterwards (see description above), or they have only a local effect without absorption. In the latter case, the API does not enter the blood stream and is excreted through the skin pores. Subsequently, it is either washed off while bathing, or can contaminate clothing. For the model, we assume that the unabsorbed fraction of the API enters the waste water in both cases i.e. either through washing of the clothes or bathing of the body.

The amount of API that is partly or completely washed off and directly emitted to the waste water as parental compound is calculated according to Eqs. (11) and (12):

$$API_{Washed\ off} = DDD \times TP \times (1-A)\ \text{(if API is partly absorbed)} \quad (11)$$

$$API_{Washed\ off} = DDD \times TP\ \text{(if no absorption occurs)} \quad (12)$$

The overall mass of parental API in the waste water influent results from the amount of unused and irregular disposed API ($API_{Irregular\ disposal}$) as well as the unabsorbed ($API_{Washed\ off}$) and absorbed ($API_{abs\_par,excreted}$) fractions (Eq. (13)):

$$API_{Influent}(\text{parental compound}) = API_{Irregular\ disposal} + API_{Washed\ off} + API_{abs\_par,excreted} \quad (13)$$

If no absorption occurs, the total amount of API_{Admin} is washed off and enters the STP. Hence, $API_{Influent}$ (parental compound) corresponds to the sum of $API_{Washed\ off}$ (or rather API_{Admin}) and $API_{Irregular\ disposal}$. The amount of metabolite *i* in the STP influent is calculated according to Eq. (10).

After the API is washed off and/or excreted, it enters the EoL phase as parental compound or metabolite *i* as part of the STP influent.

Specific assumption:

- We do not differentiate between wash off via shower or residues on clothes that are washed afterwards

3. Pharmaceuticals for pulmonary application with/without absorption:

Pharmaceuticals for pulmonary application are divided into gaseous (e.g. anaesthetic gases) and other forms of administration (e.g. aerosols as asthma inhaler). Gases are assumed to be absorbed after inhalation by alveoli. They are not excreted with urine or faeces but eliminated withershins and usually exhaled in their parental form (Langner et al. 2011; Sherman et al. 2012). Thus, the exhaled fraction $API_{Exhaled}$ (see flow 3 according to Table 2) is considered as an elementary flow to the environment i.e. the surrounding air and corresponds to the initial inhaled fraction (see Eq. (14)):

$$API_{Exhaled} = DDD \times TP \quad (14)$$

If other forms such as aerosols are assessed, the API can be partly absorbed and excreted via urine or faeces. Therefore, Eqs. (6), (7) to (8) shall be used to determine $API_{Influent}$. The unabsorbed fraction, however, is assumed to be exhaled as parental compound (Hirsch 2019):

$$API_{Exhaled} = DDD \times TP \times (1-A) \quad (15)$$

Because $API_{Exhaled}$ is an elementary flow, no further treatment needs to be considered in the EoL phase.

Specific assumptions:

- For gaseous applications (e.g. anaesthetic gases), the API is either partly exhaled (without absorption) or absorbed, distributed, eliminated and exhaled afterwards. In sum, however, the released fraction corresponds to the initial inhaled fraction. Both the unabsorbed and absorbed fractions of the pulmonary pharmaceutical are completely eliminated via breathing air. Hence, $API_{Exhaled}$ is an elementary flow to air. Furthermore, no metabolization is assumed.
- For other pulmonary applications (e.g. aerosols), it is assumed that the unabsorbed fraction is completely exhaled in parental form.
- If pulmonary application forms are assessed, the irregular disposal of these specific pharmaceuticals via sinks and toilets is assumed to not take place given that these pharmaceuticals are usually packaged in a specific container (e.g. inhaler or gas cylinder) that must be disposed of otherwise.

3.2.2 EoL phase

After use, the API enters the EoL phase in its parental or metabolized form. Within the EoL phase, it is distinguished between administered (used) pharmaceuticals (including irregularly disposed products) which enter the waste water stream ($API_{Influent}$ for parental compound and each metabolite *i*, hereinafter collectively referred to as '$API_{Influent}$'), and

unused products that are regularly disposed. The modelling approaches are presented in the following sections.

EoL of administered pharmaceuticals—behaviour of the API in STP In Germany, it can be assumed that the majority of the households are connected to a STP (see chapter 3.1). Moreover, it is assumed that the waste water flow enters the STP without any dilution between the PoE and the STP as a worst case scenario.

After entering the STP, the API included in the waste water can be removed by bacteria (if it is biodegradable), accumulate in the solid phase i.e. the sewage sludge ($API_{Solid\ matter}$, see flow 6 according to Table 2), evaporate to air ($API_{Evaporated}$, see flow 8 according to Table 2) or persist and remain in the liquid phase ($API_{Effluent}$, see flow 5 according to Table 2). Based on the concept of 'mass balance', Eq. (16) describes the correlation between STP inputs and outputs, whereas $API_{Effluent}$ and $API_{Evaporated}$ represent elementary flows, while $API_{Solid\ matter}$ is further processed as part of the sewage sludge and either disposed or used in another life cycle (e.g. as fertilizer):

$$API_{Influent} = API_{Effluent} + API_{Solid\ matter} + API_{Evaporated} \quad (16)$$

To model the behaviour of the API in the STP and determines the amount of the API contained in the different STP compartments (i.e. solid matter, air, water), we propose to apply either (1) average literature values, such as empirical data on biodegradability of an API and the binding characteristics to solid matter within the STP (e.g. Hörsing et al. 2011; Radjenović et al. 2009; Stevens-Garmon et al. 2011; Tiwari et al. 2017), or (2) existing estimation tools such as SimpleTreat 4.0 by the Dutch National Institute for Public Health and the Environment (RIVM). Simple Treat 4.0 is a steady-state non-equilibrium multimedia model that is based on the fugacity concept by Mackay (1979). It enables to estimate the fate of a pharmaceutical in a conventional activated sludge STP in the European Union (Struijs 2013). If the SimpleTreat model is used, we recommend to apply SimpleTreat 4.0 instead of v. 3.1 because the early version of the tool revealed several weaknesses if pharmaceuticals (or rather ionized or polar substances at a neutral pH) are analyzed (Franco et al. 2013a, 2013b; UBA 2015).

For using the SimpleTreat model, physical-chemical parameters (e.g. molecular weight, vapour pressure, water solubility, octanol-water partition coefficient) are needed (European Commission 2003). These input data (so called 'base-set data') can be determined by using field data. Alternatively, if this data is not available, different free and commercial tools can be applied to gather information on molecular descriptors or to predict physical-chemical properties based on Quantitative structure–activity relationship (QSAR) models (ECHA 2019). For the latter, estimation tools such as EPI Suite™ developed by the US EPA (US EPA 2012) can be used.

As the SimpleTreat tool is commonly used within risk assessment studies, it provides results as (1) concentrations in the different STP compartments (e.g. air, raw and settled sewage, effluent), and (2) elimination and emission rates for the different STP processes (e.g. elimination in the aerator, emission to effluent). To make the SimpleTreat results applicable in an LCA context i.e. to relate all API flows and emissions to the FU, only the elimination and emission rates are utilized as 'distribution factors (DF)' which describe the share of API or metabolite *i* that is emitted to the different STP compartments. The DF are applied to the results from the use phase by multiplying them with $API_{Influent}$ (see Eqs. (17), (18) to (19)):

$$API_{Effluent} = API_{Influent} \times DF_{Liquid} \quad (17)$$

$$API_{Solid\ matter} = API_{Influent} \times DF_{Solid\ matter} \quad (18)$$

$$API_{Evaporated} = API_{Influent} \times DF_{Gaseous} \quad (19)$$

Specific assumptions:

- Inherent assumptions of the SimpleTreat model shall be considered (see Struijs (2014) and UBA (2015) for further information)
- Households and other PoEs are connected to a STP
- No dilution between PoE and STP (worst case scenario)

EoL of unused products As described in chapter 3.1, the majority of unused pharmaceuticals enter the waste stream with other waste fractions and are incinerated afterwards. The incineration of non-hazardous residual waste takes place at a temperature of > 850 °C according to the German legislation (Bund 2019). Cytostatic drugs, however, are an exception as they are classified as hazardous waste. Thus, they are collected separately and incinerated in hazardous waste incineration plants at temperatures > 1100 °C. Consequently, the API is either completely inactivated or thermally destroyed during these processes (BMG 2018; Bund 2014). In some cases, residual waste is further treated in a mechanical-biological treatment plant and partly incinerated or disposed on a landfill. The treated waste, however, is expected to be inert after thermal or mechanical-biological treatment (UBA 2018a). For the example of Germany, we assume that the API emission to water ($API_{Waste\ disposal\_water}$), soil ($API_{Waste\ disposal\_soil}$) and air ($API_{Waste\ disposal\_air}$) (flows 9 to 11 according to Table 2) from the waste incineration process or landfill activities are very small (see Eq. (20)). The potential insignificance of API emissions due to landfill or waste incineration is also mentioned by Cook et al. (2012).

$$API_{Waste\ disposal\_water} = API_{Waste\ disposal\_soil} = API_{Waste\ disposal\_air} \approx 0\ mg \quad (20)$$

Specific assumptions:

- No leakage occurs during the residual waste processing before incineration
- The regular disposal pathway via residual waste is assumed to be applicable for Germany
- Pharmaceutical compounds are assumed to be inactivated or thermally destroyed during incineration process at temperatures > 850 °C
- API emissions to the environment due to disposal on landfills are expected to be very small because the overall amount of pharmaceuticals entering this waste stream is expected to be extremely low (UBA 2018b) and in Germany, pharmaceuticals are not disposed on landfills without pre-treatment in a mechanical-biological treatment plant. Potential API emissions occurring from the mechanical-biological treatment are also assumed to be negligible due to the intense processing of the residual waste, such as pre-sorting, closed-loop circulation of process water and post-combustion of gaseous emissions (Braatz 2019).

3.3 Model application to the example of ibuprofen

To test the applicability of the model, we carry out an exemplary calculation for ibuprofen based on publically available data. As the substance-specific pharmacokinetic data (e.g. absorption rate, metabolization rate) and the data needed for the SimpleTreat calculation (e.g. octanol-water partition coefficient Kow, Henry coefficient H, biodegradation constant k biodeg) vary significantly among the literature, we mostly use average values, or single values if information on the certain parameter is scarce. By doing so, we are able to model the use and EoL phase i.e. to determine all elementary flows referred to the FU and the corresponding reference flow. As only few information on pharmacokinetic properties of metabolites or transformation products are publically available, only the EoL of the parental compound and its behaviour in the STP is calculated in this example.

In the following, all API flows and emissions according to Table 2 are calculated by applying the equations described in chapters 3.2.1 and 3.2.2. The specific data sources and results are illustrated in Table 3:

The distribution of ibuprofen within the use and EoL phase is summarized and illustrated in the following Sankey diagram (see Fig. 2). All values are referred to the total amount of API (8820 mg) i.e. the sum of administered (8400 mg) and unused (420 mg) ibuprofen:

Here, ibuprofen is partly disposed as residual waste ('Disp'), the majority of ibuprofen is metabolized ('Meta 1 and 2'). The parental compound ('Parent') from both excretion and irregular disposal is mainly removed by biodegradation ('Degrad') after entering the STP. A marginal share accumulates in solid matter ('Solid'), whereas the gaseous emission pathway is negligible in this example. However, a significant share of the overall amount of API is expected to remain in the effluent and subsequently enters the surface water body ('Effluent').

Furthermore, a small proportion of the initial dose are not clearly assigned to a certain API flows or emission (not characterized, 'NC') due to different reasons: First, we only consider two main metabolites representing a metabolization rate of 86% of the administered and absorbed amount of API, whereas several studies state a higher metabolization rate > 90% (e.g. Pubchem (2019)). Second, the use of different data sources for excretion and metabolization rate can lead to deviations in the mass balance.

These relations are also confirmed if the fate of the API is calculated separately for the administered and unused fraction:

Referred to the administered product (reference flow of 8400 mg ibuprofen), about 73.1% of the API are metabolized, 22.65% are excreted as parental compound and 4.25% are not characterized. The parental compound enters the STP where the major part is biodegraded (about 13.94%). About 8.35% remain in the effluent and a small share (about 0.36%) accumulates in solid matter. Evaporation during waste water treatment is negligible for this example.

The unused fraction (420 mg ibuprofen, see Table 3) is mainly disposed regularly (85%), whereas 15% are assumed to be disposed irregular via sinks and toilets where the API enters the waste water flow. In the STP, about 9.23% of the irregular disposed API are biodegraded, 0.24% enter sewage sludge and 5.53% are emitted to the environment via effluent. Similar to the administered fraction, evaporation of the API in the STP does not occur.

4 Discussion

The purpose of this work is to provide a simplified, yet comprehensive and applicable life cycle inventory model to estimate all API emissions that occur during the use and EoL phase of a pharmaceutical product. In the following chapters, the completeness (see chapter 4.1), general and specific assumptions (see chapter 4.2) as well as the applicability of the proposed model (see chapter 4.3) are discussed.

Table 3 Application of the model to the example of ibuprofen

Flow #	Calculation (ibuprofen, 400 mg)	Data source/reference
1	$API_{Admin} = 1200\ mg \times 7\ day = 8400\ mg\ (oral) \triangleq 21$ tablets	TP is individually determined, DDD obtained from DIMDI (2019)
2	$API_{Unused} = 8400\ mg \times 0.05 = 420\ mg$	Loss rate at consumer: 5% for healthcare products (European Commission 2018)
	$API_{Regular\ disposal} = 420\ mg \times 0.85 = 357\ mg$ $API_{Irregular\ disposal} = 420\ mg \times 0.15 = 63\ mg$	Average disposal rates for solid products according to Bartsch (2010) applied to API_{Unused}
3	Not applicable (n/a) because the model is tested for oral application of ibuprofen (see Table 1)	
4	$API_{nabs\_par,\ excreted} = 0.09 \times 8400\ mg \times 0.85 = 643\ mg$	Excretion rate: Medsafe (2017), absorption rate A: Ortiz de García et al. (2013)
	$API_{abs\_met\ 1,\ excreted} = 8400\ mg \times 0.85 \times 0.35 = 2499\ mg$ $API_{abs\_met\ 2,\ excreted} = 8400\ mg \times 0.85 \times 0.51 = 3641\ mg$	Metabolization rate for metabolite 1 and 2[1]: Medsafe (2017)
	$API_{nabs\_par,\ excreted} = 8400\ mg \times (1 - 0.85) = 1260\ mg$	Excretion rate: Medsafe (2017), absorption rate A: Ortiz de García et al. (2013)
	$API_{Influent}(parental) = 63\ mg + 643\ mg + 1260\ mg = 1966\ mg$ $API_{Influent}(metabolite\ 1) = API_{abs\_met\ 1,\ influent} = 2499\ mg$ $API_{Influent}(metabolite\ 2) = API_{abs\_met\ 2,\ influent} = 3641\ mg$	See calculations for $API_{Irregular\ disposal}$, $API_{abs\_par,\ excreted}$ and $API_{nabs\_par,\ excreted}$
5, 6, 8	$API_{Effluent} = 1965.6\ mg \times 0.3687 = 724.72\ mg$ $API_{Solid\ matter} = 1965.6\ mg \times 0.0159 = 31.25\ mg$ $API_{Evaporated} = 1965.6\ mg \times 0 = 0\ mg$ $API_{Degraded} = 1965.6\ mg \times 0.6154 = 1209.63\ mg$ Removal rate = 63.13%	DF and removal rate calculated with SimpleTreat4.0. A detailed overview on the calculation parameters used in SimpleTreat can be found in the supplementary material (Tables S1–3).
7	Not applicable (n/a) because the application of sewage sludge as fertilizer is outside the scope of this publication	
9–11	$API_{Waste\ disposal\_water} = API_{Waste\ disposal\_soil} = API_{Waste\ disposal\_air} = 0\ mg$	See chapter 3.2.2

[1] In this example, ibuprofen is mainly metabolized to two substances: 2-4-(2-hydroxy-2-methylpropylphenyl) propionic acid (metabolite 1) and 2-4-(2-carboxypropylphenyl) propionic acid (metabolite 2) (Davies 1998; Medsafe 2017). Therefore, only these two metabolites are considered

4.1 Completeness and transferability of the model

The qualitative model contains all major API flows and emissions that can occur during the use and EoL phase (see Table 2). It is based on scientific literature and expert knowledge, and provides the basis for the quantification of each flow. The quantitative model (see chapter 3.2) is proposed for a chosen geographic scope and distinguish between relevant application forms and are valid for the majority of pharmaceutical products for human use. Few exceptions e.g. cytostatic drugs and hormones should be tested separately and reassessed due to their specific toxicity and/or pharmacokinetic behaviour. The model is applicable for parental compounds as well as metabolites and transformation products if data on the formation processes, pharmacokinetic and chemical-physical properties are available. As a result, it can be presumed that the model is highly transferable to other pharmaceuticals and application forms by introducing different potential use and EoL scenarios. Furthermore, most aspects of the model can be easily applied to other regions (especially for European countries), whereas some adjustments are needed e.g. the user waste disposal behaviour, the STP technology (if applicable) and EoL scenario for unused pharmaceuticals (see also chapters 4.2.2 and 4.2.3). However, this could be particularly challenging for developing countries where no reliable waste management exist, or no appropriate data regarding the use and EoL phase might be available.

4.2 Assumptions and limitations of the model

In the following, the limitations and assumptions of the model are critically reflected and discussed whereby data availability as well as the restriction of the geographic scope can be seen as the most limiting aspects.

4.2.1 Application of pharmaceuticals and behaviour in the human body

The pharmacokinetic behaviour in the body depends on several complex interactions, such as the state of health, food intake, application of other pharmaceuticals and blood circulation. Moreover, some publications reveal that gender-specific data could be relevant e.g. if the use of hormones is assessed (e.g. Carballa et al. 2008; Johnson and Williams 2004; Ortiz de García et al. 2013). Publically available literature, however, usually does not consider these specifications and reveals inconsistencies with regard to the experimental design used to obtain the data. Therefore, we propose to use

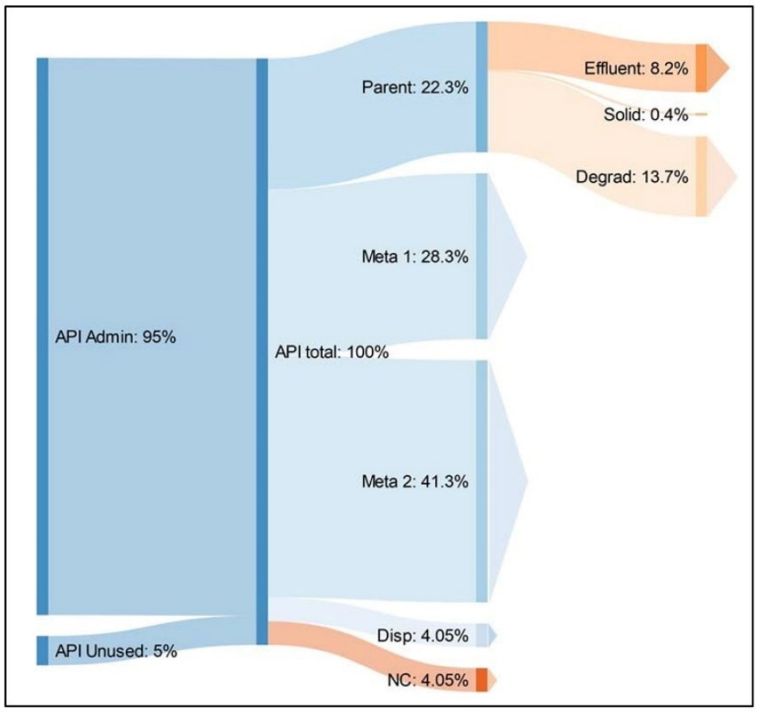

Fig. 2 Distribution of ibuprofen within the use and EoL phase (Sankey diagram)

either average values or worst case scenarios, and to evaluate the influence of these pharmacokinetic parameters (i.e. absorption rate, metabolization rate, excretion rate) by performing a sensitivity analysis.

Moreover, the elimination process within the body depends on different time-dependent aspects e.g. bioavailability, clearance and elimination half-time. In this model, however, we assess a cumulative (static) state where the body is considered as a black box model. Thus, all calculations regarding the pharmaceutical behaviour in the body are based on the total amount of API that is administered during the TP.

In reality, however, the eliminated amount of API per time unit is probably much lower. Using concentrations instead of absolute values is important, if dilution effects and degradation processes in an STP are modelled. As a result, calculated values according to the proposed LCA model probably overestimate API emissions compared with actual excretion data.

4.2.2 EoL of administered pharmaceuticals

One model parameter which is significantly determined by the geographic scope is the emission of an API to waste water after use or irregular disposal. Here, we presume that waste water from healthcare facilities and households is treated in a STP. This assumption is valid for the majority of the German households (see also chapter 3.1) but on a global scale, the majority of countries release their waste water directly to the environment without any treatment in an STP (WWAP 2017). However, if contaminated waste water is not treated in STP, it is usually directly emitted to natural environment (surface water or soil/ground water). Hence, the behaviour of an API in STP would be omitted. This adjustment simplifies the model and therefore decreases the uncertainty of the overall results.

Moreover, this model parameter also depends on the region-specific wastewater treatment technology. This waste water treatment scenario and its calculation with SimpleTreat is feasible for most of the European countries, but probably limited regarding its application for other regions without proper ST technologies. Moreover, the SimpleTreat model cannot be modified (UBA 2015) and thus, advanced technologies (e.g. ozonization) to remove pharmaceuticals or other micropollutants cannot be considered which can probably lead to an overestimation of the API emission to surface water. To overcome these obstacles, we propose to define default values for the share of untreated and treated waste water. If the water remains untreated, it can be assumed that the full amount of API reaches the respective water bodies. If the waste water is treated, however, removal rates and distribution factors for each API need to be individually calculated based on region-specific STP technologies. To our knowledge, however, experimental data obtained from peer-reviewed literature only describe removal rates in STPs and not the distribution factors which can lead to an underestimation or false interpretation of API emission pathways.

It shall also be noted that this estimation model illustrates an ideal situation. In reality, however, several reactions can change the amount of metabolites and parental compounds. For instance, Alder et al. (2010) describe the reversion of propranolol to its parental compound due to hydrolysis in the STP even if the substance is previously metabolized in the body. Furthermore, photodegradation in surface water as well as indirect photolysis can also have a significant influence on the overall mass of APIs in environmental compartments. These substance-specific characteristics are not yet included in the model but should be taken into account in future calculations. In addition, dilution effects, technical malfunctions within the STP or weather events such as heavy rain can also lead to variations in the results.

4.2.3 EoL of unused pharmaceuticals

The model contains a default waste disposal scenario (i.e. regular disposal via residual waste, default disposal rates) that appears to be valid for Germany. However, other countries may stipulate or provide other options to dispose of unused/expired pharmaceuticals (e.g. state-runned take-back schemes), or patient disposal behaviour differs due to education or environmental awareness. As a result, the disposal pathway as well as the default disposal rates for regular/irregular disposal should be re-assessed and adjusted for different regions, if data is available.

To consider the disposal of unused/expired products in the model, product waste/loss rates (at consumer) are included. However, the default values according to PEF should be critically reflected because PEF does not explicitly mention pharmaceuticals as a potential product category but only lists the retail sector ('healthcare'). Thus, product-specific aspects which could have an influence on the amount of product waste (e.g. type of disease i.e. chronic/acute, as well as TP, DDD and packaging sizes) are probably not properly reflected. In addition, we assume the same loss rate for private households and healthcare facilities which can be questioned due to a demand-driven procurement strategy in healthcare facilities. The overall influence of these aspects on the amount of product waste needs to be further examined in a representative study and should be specified.

The irregular disposal of pharmaceuticals represents a significant entry pathway of APIs to the natural environment (Kinrys et al. 2018). Here, we assume that irregular disposal only takes place at households. Although there is also a potential risk in healthcare facilities for irregular drug disposal, this emission pathway is presumed to be negligible based on expert knowledge (BVL 2018). However, reliable data do not exist. Moreover, we assume that 100% of the irregular disposed API enters the sewer system and reaches the STP as parental compound. But in some cases, the API is pharmacologically inactivated after exceeding the expiration date. In addition, several studies (e.g. O'Brien et al. 2017; Thai et al. 2014) mention degradation processes within the sewer system that can significantly affect the amount of a chemical compound in the STP influent. Consequently, these assumptions describe worst case scenarios and may lead to an overestimation of the amount of $API_{Influent}$ (especially if biodegradability of the API is high). Computational fluid dynamics (CFD) and other hydrological/hydrodynamic models could provide useful information on dilution and degradation processes within the sewer system.

For unused products which are disposed regularly, we assume that they are collected as residual waste or non-hazardous industrial waste, treated and incinerated afterwards. This scenario is also applicable for API contained in solid matter from STP, which is either further processed and incinerated or treated and used as fertilizer in a new life cycle. In both cases, it is assumed that the API is inactivated or thermally destroyed. However, this EoL scenario strongly depends on the geographic scope of the study. The requirements for combustion processes to incinerate residual waste and non-hazardous commercial waste is based on the Directive 2000/76/EC of the European Parliament and of the Council of December 4, 2000 on the incineration of waste (EU 2000). As a result, it is presumed that the assumption is also applicable for other European countries.

Landfill as an alternative EoL scenario, however, should be carefully considered for other regions. In other countries, unused pharmaceuticals could be disposed as municipal waste that enters the landfill body without further treatment. Here, the API can be biotransformed and partly converted into landfill gas, sorbed to solid matter and be retained in the landfill or dissolved and enter the leachate (Cook et al. 2012). Several studies emphasize the risk of potential pharmaceutical emission originating especially from leachate (e.g. Masoner et al. 2016; Qi et al. 2018). Consequently, the magnitude of these flows depends on the country-specific waste management practices and needs to be determined individually. For Germany, however, the risk of pharmaceuticals entering the environment via untreated leachate is expected to be negligible due to mechanical-biological pre-treatment of waste streams and sealing systems for landfill bodies (BMG 2018) although the data availability for the fate of pharmaceuticals in this particular processes is very low.

4.3 Applicability of the model

The model appeared to be feasible and applicable for the case of ibuprofen since all API flows and emissions are calculated with publically available data. However, the application of the model also reveals two major challenges:

First, there is a general overarching problem of data availability, especially for metabolites which can significantly contribute to the overall API emissions (in the case of ibuprofen,

about 90% of the parental compound are metabolized). Metabolites can also have an adverse effect in the environment (Celiz et al. 2009). Their exclusion can thus lead to incomplete impact assessment results and therefore metabolites should be generally considered in LCA studies. However, environmental data (such as biodegradation rates) is hardly available for metabolites, mainly due to analytical challenges (Langford and Thomas 2011). To accurately reflect environmental risks and burdens of pharmaceuticals and their emissions into the environment, collecting data on metabolites (e.g. on their behaviour in the environment or their effect on wildlife species) must just as much become a priority in science and regulatory toxicology as data on them will improve many of the existing models and thus allow a more accurate assessment of risks and burdens associated with pharmaceutical substances. An additional challenge with regard to data is the lack of harmonized data sets in the pharmaceutical sector which results in an enormous variation of data on pharmacokinetic and chemical-physical properties.

Second, the results for $API_{Effluent}$, $API_{Solid\ matter}$ and $API_{Evaporated}$ are hardly comparable with values (i.e. PEC or MEC) from existing literature due to the reference to the FU. In addition, most of the studies evaluate the concentrations of pharmaceuticals in surface water or sewage sludge whereas only few studies consider the API emission to air. Thus, the representativeness and plausibility of these results are difficult to assess.

Nevertheless, the calculation of the fate of the pharmaceutical product in the body appeared to be plausible since several sources provide similar data on metabolization, absorption and excretion of ibuprofen. Furthermore, according to Smook et al. (2008), the calculated removal rate of 63% is expected to be realistic compared with other studies that mention removal rates for ibuprofen between 60 and 99%. The feasibility of using SimpleTreat to assess the fate of pharmaceuticals in the STP is also discussed in Lautz et al. (2017). According to the authors, SimpleTreat appears to be feasible to determine the concentration of pharmaceuticals in the effluent, whereas the prediction of the amount of an API contained in the secondary sludge is mostly underestimated. Here, Lautz et al. (2017) suggest to employ average measured data rather than results from SimpleTreat. This becomes obvious if the example presented herein is compared with the results obtained by Cook et al. (2012): The overall removal rate is similar, but the amount of API contained in sludge is significantly lower for the example calculated with SimpleTreat. Therefore, the results obtained with SimpleTreat should be treated with caution and validated based on average empirical data. Furthermore, neglecting dilution effects between PoE and STP or other degradation processes in the sewer and STP can probably lead to an overestimation of the results for API emissions to surface water.

Moreover, Cook et al. (2012) confirm that ibuprofen is thermally destroyed after incineration, which is in alignment with the assumption made in this study. Landfill leachate, however, can be a potential source for API emissions into the environment. Yet, in the case of ibuprofen specifically, the risk from landfill leachate was deemed to be low. While Cook et al. (2012) attribute this low risk to the high sorption rate (75–100%) of ibuprofen to the municipal waste, we assume it to be the result of the waste pre-treatment step taking place in Germany as well as the treatment of landfill leachate. Despite the similar conclusions drawn in both studies in relation to Ibuprofen, the explanation and reasoning behind them is thus fundamentally different due to the divergent geographical scope and the related differences in waste management techniques (Maplecroft 2019).

5 Conclusions

Although there is a scientific consensus on the ecotoxic potential of released pharmaceuticals, current LCA studies do not include the use and EoL phase where most of these API emissions arise. Therefore, we propose a comprehensive, yet applicable inventory model to calculate emissions of APIs during/after the application and disposal of pharmaceutical products.

For this purpose, we describe these life cycle phases on a qualitative level based on existing literature and expert knowledge. All potential API flows and emissions are identified. Second, calculation procedures are provided for each flow based on the risk assessment approach. Furthermore, strategies to limit the complexity of the model are proposed to increase its practicality. In addition, the model is exemplarily tested for ibuprofen.

The qualitative model contains all major API emission sources, including the risk of irregular disposal of unused/expired pharmaceuticals via sinks or toilets. Furthermore, the user can distinguish between different forms of application. The model is instantiated only for Germany/Europe but its basic principles can be adapted for and transferred to other regions.

The example of ibuprofen revealed that all flows for the parental compound can be calculated with publically accessible data whereas the data availability for metabolites is very limited. The utilization of publically available data is important for the applicability in LCA case studies as practitioners may not have access to confidential detailed API-specific information e.g. in authorization documents. Ibuprofen is well studied i.e. pharmacokinetic data such as absorption rate, metabolization rate and excretion rate as well as data on chemical-physical properties to calculate its behaviour in the STP are readily available, but for other APIs the data availability can be a limiting factor.

Nevertheless, this paper also revealed some obstacles and remaining challenges:

First, future research should focus on expanding the scope with regard to the product category and the geographic validity. We propose to adjust the model to similar product categories e.g. veterinary medicine, and to make the model also applicable for other countries by modifying the region-specific assumptions and limitations. In this context, we strongly suggest to provide more harmonized, reliable and publically available data (e.g. on pharmacokinetic properties, patient disposal behaviour and degradation processes in the sewer system), and to further develop the SimpleTreat model to make it also applicable for other (regionalized) STP technologies.

Second, specific modelling rules may be needed for some pharmaceuticals such as anticancer drugs or hormones. For instance, aspects such as potential risks caused by unintended exposure of a human being due to human-human interaction (e.g. if anticancer drugs are applied) need to be critically reflected in future impact assessment approaches.

Third, additional calculation approaches should be developed to include the environmentally relevant aspect of using sewage sludge as fertilizer since this could be a predominant source for API emissions. The estimation of API contained in sewage sludge, however, is a challenging task due to potential degradation and transformation processes during sludge treatment.

Therefore, the proposed model will be further applied and refined by assessing other highly prioritized pharmaceuticals where data is publically available. Here, one focus could be on semi-volatile APIs and other application forms to evaluate the reliability of the model. For this purpose, a comprehensive case study is currently conducted with partners from the pharmaceutical industry and will be addressed in a subsequent paper.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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CORRECTION

Correction to: Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment

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Correction to: The International Journal of Life Cycle Assessment
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The original version of this article unfortunately contained a mistake which was missed during typesetting. In Tab. 3, the first parameter of Flow #4 was incorrect. The correct version of the table is given below.

The original article has been corrected.

The online version of the original article can be found at https://doi.org/10.1007/s11367-019-01722-7

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Table 3 Application of the model to the example of ibuprofen

Flow #	Calculation (ibuprofen, 400 mg)	Data source/reference
1	$API_{Admin} = 1200\ mg \times 7\ day = 8400\ mg\ (oral) \triangleq 21$ tablets	TP is individually determined, DDD obtained from DIMDI (2019)
2	$API_{Unused} = 8400\ mg \times 0.05 = 420\ mg$	Loss rate at consumer: 5% for healthcare products (European Commission 2018)
	$API_{Regular\ disposal} = 420\ mg \times 0.85 = 357\ mg$ $API_{Irregular\ disposal} = 420\ mg \times 0.15 = 63\ mg$	Average disposal rates for solid products according to Bartsch (2010) applied to API_{Unused}
3	Not applicable (n/a) because the model is tested for oral application of ibuprofen (see Table 1)	
4	$API_{abs\_par,\ excreted} = 0.09 \times 8400\ mg \times 0.85 = 643\ mg$	Excretion rate: Medsafe (2017), absorption rate A: Ortiz de García et al. (2013)
	$API_{abs\_met\ 1,\ excreted} = 8400\ mg \times 0.85 \times 0.35 = 2499\ mg$ $API_{abs\_met\ 2,\ excreted} = 8400\ mg \times 0.85 \times 0.51 = 3641\ mg$	Metabolization rate for metabolite 1 and 2[1]: Medsafe (2017)
	$API_{nabs\_par,\ excreted} = 8400\ mg \times (1 - 0.85) = 1260\ mg$	Excretion rate: Medsafe (2017), absorption rate A: Ortiz de García et al. (2013)
	$API_{Influent}(parental) = 63\ mg + 643\ mg + 1260\ mg = 1966\ mg$ $API_{Influent}(metabolite\ 1) = API_{abs\_met\ 1,\ influent} = 2499\ mg$ $API_{Influent}(metabolite\ 2) = API_{abs\_met\ 2,\ influent} = 3641\ mg$	See calculations for $API_{Irregular\ disposal}$, $API_{abs\_par,\ excreted}$ and $API_{nabs\_par,\ excreted}$
5, 6, 8	$API_{Effluent} = 1965.6\ mg \times 0.3687 = 724.72\ mg$ $API_{Solid\ matter} = 1965.6\ mg \times 0.0159 = 31.25\ mg$ $API_{Evaporated} = 1965.6\ mg \times 0 = 0\ mg$ $API_{Degraded} = 1965.6\ mg \times 0.6154 = 1209.63\ mg$ Removal rate = 63.13%	DF and removal rate calculated with SimpleTreat4.0. A detailed overview on the calculation parameters used in SimpleTreat can be found in the supplementary material (Tables S1–3).
7	Not applicable (n/a) because the application of sewage sludge as fertilizer is outside the scope of this publication	
9–11	$API_{Waste\ disposal\_water} = API_{Waste\ disposal\_soil} = API_{Waste\ disposal\_air} = 0\ mg$	See chapter 3.2.2

[1] In this example, ibuprofen is mainly metabolized to two substances: 2-4-(2-hydroxy-2-methylpropylphenyl) propionic acid (metabolite 1) and 2-4-(2-carboxypropylphenyl) propionic acid (metabolite 2) (Davies 1998; Medsafe 2017). Therefore, only these two metabolites are considered

3.3 Case study of an ibuprofen analgesic from cradle to grave

This chapter contains the following publication:

- Siegert M.-W., Saling P., Mielke P., Czechmann C., Emara Y., Finkbeiner M. **Cradle-to-grave life cycle assessment of an ibuprofen analgesic**. Sustainable Chem. Pharm. **18**, 100329 (2020). https://doi.org/10.1016/j.scp.2020.100329

In this publication, the methodological rules for pharma-LCAs (first publication) as well as the model to include the use and EoL stage (second publication) are combined and incorporated in a case study on an ibuprofen analgesic.

The goal of the study is to assess the potential environmental impacts of Eudorlin® Extra (coated tablets in a PVC/aluminum blister) from cradle to grave.

For this purpose, the production (API manufacturing, galenic formulation and packaging), the use of the pharmaceutical as well as its EoL are taken into account. The functional unit is defined as the treatment of an adult in Germany with the purpose of pain relief for 4 days, the reference flow is one package Eudorlin® Extra (10 tablets with 400 mg ibuprofen per tablet). Primary data for the API production, galenic formulation, packaging and distribution is gathered from the manufacturing companies BASF (API production) and Berlin Chemie (galenic formulation, packaging distribution). Background data for the production stage is either collected and utilized from commercial databases such as GaBi and Evoinvent, or estimated by combining existing process design approaches with stoichiometric and thermodynamic calculations. Transportation activities are included by using default data on transport distances, types and utilization of vehicles. To consider API emissions occurring from the use and EoL, the approach presented in the second publication is applied to predict the emissions of the parental compound and its metabolites from the WWTP. Non-API emissions from waste water treatment and disposal activities are modelled by linking respective elementary flows with aggregated datasets from GaBi.

The impact assessment is performed for the categories ‘climate change’, ‘human toxicity’, ‘ecotoxicity’, and ‘abiotic depletion’. The interpretation is performed by determining the environmental hot spots for each life cycle stage, and conducting a sensitivity analysis on a unit process level.

The assessment reveals that the production stage is the largest contributor to all environmental impacts, whereas the share of the use and EoL stage is rather low. This can be explained by the high material input during the manufacturing on the one hand, and a high metabolization rate of ibuprofen and its good degradability in the WWTP on the other hand. However, the case study also reveals some methodological challenges, such as missing characterization factors (CF) for the metabolites of

ibuprofen, redundant elementary flows within aggregated datasets, and strong variability among published data on ibuprofen (e.g. biodegradation rate).

The supplementary material to this publication is presented in Appendix A. 3. Supplementary material to publication 3. It comprises the following information:

- Pharmacokinetic data for ibuprofen and its main metabolites
- Input parameters ('base-set data') for the calculation with SimpleTreat 4.0
- Modelling assumptions (for production, distribution, use and EoL stage)
- Additional Life Cycle Impact Assessment (LCIA) results for Eudorlin® Extra (absolute and relative values)
- Environmental heat map for the galenic formulation

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Cradle-to-grave life cycle assessment of an ibuprofen analgesic

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ABSTRACT

Purpose: The aim is to conduct a life cycle assessment of the analgesic Eudorlin® Extra to identify environmental hotspots along its life cycle, i.e. the manufacturing of the active pharmaceutical ingredient, the galenic formulation, packaging, distribution, use and end-of-life. This publication is one of only few LCA studies that consider all life cycle stages of a pharmaceutical.
Methods: The functional unit is the treatment of an adult in Germany with the purpose of pain relief for 4 days, the reference flow is one package Eudorlin® Extra (10 tablets with 400 mg ibuprofen per tablet). Primary data is provided by the manufacturing companies for the production stage. The impact assessment is conducted for impact categories that have been identified as germane for the sector. A contribution analysis is performed and relevant processes are evaluated by sensitivity analyses.
Results and discussion: The environmental profile is dominated by the production stage whereas the use and end-of-life are negligible. This seems to be plausible due to the high material usage during manufacturing, as opposed to the use stage where no additional inputs are required. However, methodological issues are identified which potentially affect the results such as the lack of characterization factors for the metabolites.
conclusion and outlook: The results are in alignment with existing studies which emphasize the environmental relevance of the production stage. Future research should focus on improving existing impact assessment methods, developing characterization factors for metabolites and publishing inventory data on substances that are frequently used in the pharmaceutical life cycle.

1. Introduction

Pharmaceutical products are an indispensable element to facilitate a sustainable development of the global society. According to the third Sustainable Development Goal on good health and well-being, a better access to pharmaceuticals shall be assured, especially for inhabitants of developing countries (United Nations, 2020). However, numerous studies also discuss the increasing risk of the unintended release of active pharmaceutical ingredients (APIs) to the environment and their associated potential negative impacts, e.g. on wildlife (Arnold et al., 2014; Brodin et al., 2014; Strauch, 2011). Pharmaceuticals for human use can generally enter the different environmental compartments (water, soil, air) either 1) after use and subsequent excretion, wash off or exhalation, or 2) after the unused fraction is disposed of via residual waste or sinks/toilets. If the API enters the wastewater stream, it can be discharged directly to the environment or enters a wastewater treatment plant (WWTP) where the API is partly removed and emitted to water bodies (Emara et al., 2019). In the case of disposal via residual waste, the API can reach the environment e.g. via landfill leachate. This, however, strongly depends on regional conditions, such as waste management practices and consumer behavior (Boxall et al., 2012; Bu et al., 2016; Slack et al., 2005; Han et al., 2014). In addition, other (non-API) emissions and environmental impacts during the production, distribution, use and disposal of a pharmaceutical product can occur, e.g. due to resource consumption and energy use during the production stage, as well as emissions from transportation, storage and waste disposal activities. Therefore, it is crucial to consider a holistic life cycle perspective from resource extraction ('cradle') to the final disposal of the product ('grave') if the environmental performance of pharmaceutical products is assessed. The integration of life cycle thinking is also described by the ACS GCI Pharmaceutical Roundtable and other experts from the pharmaceutical sector as one key area of action to facilitate sustainable

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pharmacy (Jiménez-González et al., 2011; Sheldon, 2017).

Life Cycle Assessment (LCA) allows to systematically determine all inputs (e.g. substrates, reactants, energy etc.) and outputs (greenhouse gas emissions, wastewater etc.) as well as the related potential environmental impacts of a product system throughout the entire life cycle. LCA is an internationally recognized method and standardized by the norm series ISO 14040 published by the International Organization for Standardization (ISO) (Finkbeiner, 2013). According to ISO 14040 and 14044, an LCA study contains four phases (ISO, 2006a; 2006b):

1) Goal and scope: Describing the application and target group of the study. In addition, important methodological parameter (such as the system boundaries, the function of the product system, data requirements etc.) are defined
2) Life cycle inventory: Collecting qualitative and quantitative data on all inputs and outputs within the system boundaries
3) Life cycle impact assessment: Transforming life cycle inventory data into potential environmental impacts by applying impact assessment methods
4) Interpretation: Analyzing and interpreting the inventory and impact assessment results with regard to the goal and scope definition to derive recommendations for the audience

All inventory flows and impact assessment results are referred to the functional unit (FU), i.e. the quantified use of a product system, and the reference flow, i.e. the amount of product that is necessary to fulfil the FU (Finkbeiner et al., 2006). The results can then be used by decision makers to identify environmental hotspots of the product system, to optimize material usage and/or process design within the value chain, to compare different products or alternative manufacturing processes, or for external communication (e.g. Environmental Product Declarations).

The aim of this paper is to present a comprehensive LCA study on an ibuprofen based analgesic and to identify its environmental hotspots along the entire life cycle, i.e. the manufacturing (in particular: API production, galenic formulation and packaging), the use and EoL stage. In contrast to the majority of previously published LCAs in the sector, we therefore consider all life cycle stages of a pharmaceutical product. In addition, the high availability of latest primary data for all manufacturing processes is another distinguishing feature of this work.

Ibuprofen is a Non-Steroidal Anti-Inflammatory Drug (NSAID) which has also an analgesic and antipyretic effect (Bushra and Aslam, 2010). It is produced on a global scale and one of the most frequently prescribed NSAIDs (Bradbury, 2004; Carlsson et al., 2006; Küster and Adler, 2014). However, several studies also confirm the detection of ibuprofen and its metabolites in WWTP effluents and water bodies whereby the concentrations range from ng L^{-1} to µg L^{-1} (e.g. Ashton et al., 2004; Buser et al., 1999; Loos et al., 2008; Tixier et al., 2003).

For this study, the environmental profile (i.e. the impact assessment results) of Eudorlin® Extra film tablets is determined by combining new and existing methodological approaches on LCA from the chemical and pharmaceutical sector. Then, relevant life cycle stages and processes are identified and further assessed by a sensitivity analysis.

The results provide useful information to decision makers on the environmental performance of the intermediate/product and thus, support to identify optimization potentials within the value chain. A comparison between different products or process design alternatives is not considered in this work.

2. Material and methods

The following chapters describe the most important methodological specifications for the product system and functional unit (ch. 2.1), the life cycle inventory (ch. 2.2), impact assessment and interpretation (ch. 2.3) for the case of Eudorlin® Extra. For this purpose, the Product Category Rules (PCR) for pharmaceutical products and processes (Siegert et al., 2019a) serves as a supporting document for this LCA study. A detailed overview of all model-related assumptions can be found in the supplementary material (SM ch. 3).

2.1. Product system and functional unit

According to the goal of the study, the product system includes processes as well as related inputs and outputs within the system boundaries from a cradle-to-grave perspective, i.e. from resource extraction to the final disposal of the product:

Production: Ibuprofen is batch-wise produced in a multistep manufacturing process by BASF in Bishop, US. Afterwards, the API is transported to Berlin, GER, where the galenic formulation as well as the packaging are performed by Berlin Chemie. The final product Eudorlin® Extra comprises a film-coated tablet with 400 mg ibuprofen per tablet. It is packed in an PVC/aluminium-blister (primary packaging) containing 10 tablets, a leaflet and a folding carton (secondary packaging).

Distribution[1]: After manufacturing, the product is shipped to pharmacies in Germany where it is subsequently sold to a patient for a self-treatment at home. This scenario appears to be feasible since ibuprofen containing analgesics are over the counter (OTC)-pharmaceuticals that are frequently used for the self-medication of a variety of diseases (e.g. headache) (Sinclair et al., 2000). Transportation processes during the distribution phase (i.e. transport from manufacturer to pharmacy, and from there to the patient) as well as the disposal of unsold pharmaceuticals ('loss rates') are included in this scenario whereas storage activities during the distribution and use stage are generally excluded since no specific conditions (such as cooling) are required for Eudorlin® Extra (Medline, 2019).

Use[1]: The product is completely applied orally by the patient, the packaging (primary and secondary) is disposed of as municipal waste. In the human body, the API undergoes different pharmacokinetic processes such as absorption, distribution, metabolization and excretion.

End-of-life (EoL): After excretion, the API enters the EoL stage by being emitted to the wastewater treatment plant in its parental and metabolized form where it is partly removed. Finally, the API and its metabolites enter the natural environment as elementary flows without any further technical treatment.

The functional unit is defined as the treatment of an adult patient in Germany with the purpose of pain relief for 4 days. The defined daily dose (DDD) for this therapeutic purpose is set as 1000 mg[2] following the instructions according to the leaflet (max. DDD for ibuprofen: 1,200 mg (DIMDI, 2019)). Based on this, the reference flow is determined as 1 package of Eudorlin® Extra containing 4000 mg ibuprofen for the entire treatment period.

The overall product system and detailed information on the processes within the core system (see (Siegert et al., 2019a) for further explanation) are illustrated in Fig. 1. Here, material and energy that has not yet been transformed by human activities enter the product system (from ecosphere to technosphere) as elementary flows. Similarly, material and energy leave the product system as elementary flow without further treatment, e.g. emissions to air, water or soil.

2.2. Life cycle inventory

The life cycle inventory phase comprises the collection of qualitative and quantitative input-/output-data as well as calculation procedures and other approaches to gather information on all life cycle stages, e.g. energy demand for the production, waste generation during to the use and emissions caused by the disposal of the product. Some aspects of the life cycle, however, are excluded since they are expected to be irrelevant for the overall environmental performance, they cannot be clearly

[1] Default scenario based on the PCR.

[2] Corresponds to 2.5 tablets per day (according to the leaflet, the tablet can be easily divided).

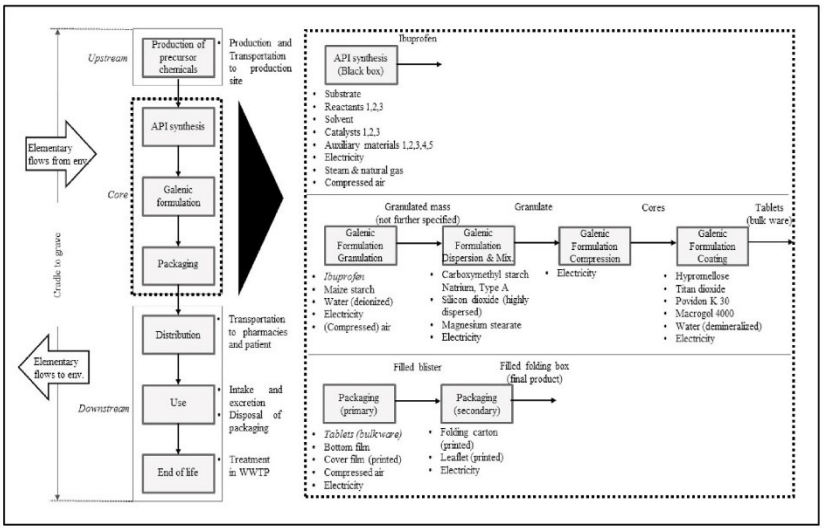

Fig. 1. System boundaries (cradle-to-grave) of the production and intake of Eudorlin® Extra For confidentiality reasons, synthesis pathways and production processes for the API production are presented as a black-box model. Furthermore, names and details on input and output materials are anonymized and referred to as an alias (e.g. reactants 1–3).

assigned to the desired product or they are part of a new product system, e.g. transport packaging, the construction of infrastructure, cleaning material or use of sanitary facilities after application of the pharmaceutical.

If recycling occurs, credits and environmental burdens are equally shared between the product system under study and the system that utilized the recycled material. This shared burden approach ('50/50 attribution method') is already used within and outside the chemical sector (EC, 2017; WBCSD, 2014).

For the life cycle inventory, different methods to generate life cycle inventory data are utilized and described in the following sections. A detailed overview of all approaches and specifications is provided in the supplementary material (Table S5).

2.2.1. Data on the production

Primary data, i.e. data that is directly provided by the process owner of the core system, is available for the API production, galenic formulation and packaging, and (partly) for the distribution of the final product on the German market. Data is collected for all inputs (i.e. substrates and other input materials, reagents, solvents, catalysts, other additives and operating materials, energy carrier and demand), outputs (i.e. intermediate products/final product, by-products, liquid and solid waste, wastewater, emissions to air, water and soil) and transportation (i.e. distances, mode of transportation and capacity). The data collection on site is executed by performing interviews, measurements and reviews of operating documents. All primary data consist of average annual values from 2019 (API production) and 2018 (galenic formulation and packaging) and are representative for the respective production site. Some data is obtained for the entire production (e.g. energy demand) and allocated to the desired product based on the production volume.

Inventory data related to background chemicals or other input materials which are purchased but not produced by the case study partner (e.g. catalysts) is considered by using aggregated datasets ('unit processes') for these substances. For this purpose, the commercial LCI database GaBi (professional and extended) v.8.7 (Thinkstep, 2020) is consulted and complemented by data obtained from the Ecoinvent database v.3.6 (Wernet et al., 2016). These datasets are also utilized to yield information on other background processes (such as energy supply) in the model. If the location of the production site of these input materials is known, region-specific datasets are used for wastewater treatment, electricity and waste disposal activities. For some substances, however, no unit processes are available in the databases. Hence, different approaches are employed to fill these data gaps:

Since information on the manufacturing process of many of these materials is usually rare or not available, inventory data is estimated by connecting existing process design approaches with basic stoichiometric and thermodynamic calculations. The selection of estimation methods for LCI generation thereby depends on the availability of data (e.g. whether information on the energy use for a specific synthesis route are available).

To gather missing inventory data for background processes on a qualitative level, the concept of a retrosynthetic breakdown (also referred to as 'chemical tree') (Ott et al., 2016) is applied. The generic synthesis route of the chemical is identified by consulting encyclopedias such as RÖMPP (Römpp, 2019) and Ullmann's Encyclopedia of Industrial Chemistry (Ullmann, 2000), patents and expert knowledge. The process should thereby reflect an industrial scale and the technological state-of-the-art to produce a particular substance. This procedure is performed for every input for which life cycle inventory (LCI) data in a commercial database does not exist. In this case, production steps are modelled until all input materials match existing datasets in the LC databases. If information on other inputs, such as catalysts, solvents, energy use, or outputs, e.g. waste generation, by-products or product losses/yield are stated, they are also considered.

The masses of material inputs are either directly obtained from literature or calculated based on the stoichiometric coefficients and linearly scaled-up to the manufacturing of 1000 kg product if this information is only available on a lab scale. This upscaling approach seems to be feasible especially for batch processes which are usually employed in the pharmaceutical and fine chemical sector (Piccinno et al., 2016). If no yield is mentioned, an efficiency of 70% is assumed over the entire reaction for all chemicals. However, if there is further information on the yield, e.g. through lab protocols, they are preferred.

To determine the energy demand (heating energy and electricity) for the production processes, the approaches presented by Piccinno et al, (2016) and Parvatker et al, (2019) are used and complemented by basic thermodynamic data if this information is available (e.g. melting enthalpy of a substance). Cooling processes are based on the data for a generic cooling tower published by Jiménez-González and Overcash (2000). Outputs from the cooling tower are either treated as wastewater (blowdown water), directly emitted to air (water evaporated) or disposed of as waste ($CaCl_2$ from ion exchange pretreatment of cooling

water).

Yield losses and by-products are both considered as waste since there is usually no information on their impurity (worst case) (Geisler et al., 2004). Other direct emissions to the environment during the production processes are represented by fugitive emissions following Jiménez-González et al, (2000).

For transportation processes, default data by (Ecoinvent, 2017) is applied to estimate transport distances as well as types and utilization of vehicles for different product groups (chemicals, waste, metallic ores, starch, plastic products and articles of base metal). Afterwards, each product group specific transportation mix is modelled with aggregated datasets from the GaBi database.

All primary and secondary data is referred to the FU and the reference flow, i.e. the intake of 4000 mg ibuprofen. The omission of chemicals or the use of proxies is avoided, if possible. If the aforementioned approaches cannot be used due to very weak data availability, datasets representing an average chemical production are utilized (Althaus et al., 2007; Hischier et al., 2005). This approach, however, was used on a very limited level because most of the data for chemical processes were available as primary data.

2.2.2. Data on the distribution, use and EoL

The generic model for the distribution, use and EoL is based on the recommendations within the PCR for pharmaceutical products and processes.

Primary data on the distribution distance and transportation mode for Eudorlin® Extra from the manufacturing site to the pharmacy is applied to the model. The transportation from the pharmacy to the point of use was considered in a way that users have a dedicated trip for purchasing the product and do not combine it with other purchases since it is assumed that pharmaceuticals are not products for daily needs.

To address the use and EoL stage, the approach by Siegert et al, (2020) is utilized. To this end, pharmacokinetic data (rates for absorption, metabolization and excretion) for metabolites[3] and the parental compound is obtained from sector-specific databases and literature (e.g. peer-reviewed studies) in the first place (see Table S1) to determine the amount of API that is excreted and enters the WWTP ($API_{Influent}$). Then, data on chemical-physical properties for ibuprofen and its metabolites is gathered from literature, databases (e.g. PubChem) or estimated with EPI Suite™, and then applied to SimpleTreat 4.0 by the Dutch National Institute for Public Health and the Environment (see Tables S2–4) to estimate the removal in the WWTP and API emissions to the environment (Siegert et al., 2020).

Non-API emissions in this case study, however, are assumed to be limited to the WWTP, disposal of packaging waste after use and the incineration of sewage sludge. Inputs and outputs related to the WWT and sludge treatment are thereby allocated based on the amount of API (parental and metabolized form) contained in the influent before and in the sewage sludge after WWT. Transportation processes for waste disposal during the use stage are modelled according to the procedure described in 2.2.1.

2.3. Impact assessment and interpretation

The impact assessment includes the selection of impact categories and characterization models, assigns the inventory results to the impact categories and results in the calculation of the environmental profile of the product system, i.e. indicator results for each impact category (ISO, 2006a; 2006b). Based on the recommendations within the PCR, the environmental impacts of the product system are analyzed for the impact categories and indicators presented in Table 1.

These impact categories and characterization models have been previously selected based on existing LCA studies from the pharmaceutical sector, the recommendations by the Product Environmental Footprint (PEF) initiative as well as an interdisciplinary workshop with different experts from the pharmaceutical sector (Siegert et al., 2019b). The selection of only few impact categories is based on the goal of the study since a limited number of impact assessment results reveals to be appropriate for internal decision making. A more detailed environmental profile is also presented in the supplementary material (see SM ch. 4).

Table 1
Impact categories, indicators and assessment models used in the case study of ibuprofen.

Impact category (indicator)	Impact assessment model
Climate change (Global warming potential, GWP)	IPCC model for GWP over a 100 year time horizon (IPCC, 2013)
Human toxicity (Human toxicity potential, cancerogenic and non-cancerogenic)	USEtox model (Rosenbaum et al., 2008, 2011)
Ecotoxicity (Freshwater aquatic ecotoxicity potential)	USEtox model (Rosenbaum et al., 2008)
Abiotic resource consumption (Abiotic depletion potential (ADP) fossil and elements)	Minerals and metals: ADP model (Guinée, 1995; van Oers et al., 2002) (ADP-elements) Energy carriers: ADP model (Guinée, 1995; van Oers et al., 2002) (ADP-fossil)

To consider the effect of ibuprofen emitted to the environment, characterization factors (CFs) for the parental compound, which were presented by Alfonsín et al, (2014), are incorporated into the GaBi software and applied as integral part of the USEtox model in this study. Hence, the freshwater aquatic ecotoxicity potential as well as human toxicity potential for the emission of ibuprofen (parental compound) to both, air and water, are taken into account for the LCIA. For the two metabolites, no CFs could be obtained and thus, their potential effects are not reflected in the LCIA results.

The interpretation is performed based on the goal and scope of the study and complementary to the environmental profile derived from the LCIA. This step supports the transparency of the results by determining the influence of significant issues, assumptions and methodological choices on the overall results. Therefore, different interpretation steps are conducted in this case study.

First, the contribution to the overall LCIA results is determined for each life cycle stage and the processes within by performing a simple ranking. Second, sensitivity analyses are performed for the environmental hotspots to identify which processes may react sensitive with regard to the overall LCIA results. To this end, significant processes are varied by ± 25% whereas other processes in the product system remain unchanged. The outcome of these interpretation steps is presented as integral part of the LCIA results in ch. 3.2.

3. Results and discussion

In the following chapters, the results for the life cycle inventory (ch. 3.1) and impact assessment (ch. 3.2) are presented and discussed.

3.1. Life cycle inventory

According to the procedure described in ch. 2.2, inventory data is gathered for each life cycle stage (i.e. production, distribution, use and EoL) and transferred to the model build in a commercial LCA software (GaBi ts v. 9.2.0.58).

3.1.1. Production

Due to confidentiality reasons, detailed information on primary data cannot be provided in this section. Nevertheless, some information on background chemicals is presented here for which no unit processes are available in the commercial data bases. These materials as well as the

[3] In this case study, we only consider the two main metabolites of ibuprofen, i.e. 2-hydroxy ibuprofen and carboxy ibuprofen Bushra and Aslam (2010).

respective references to gather information on the synthesis pathways are summarized in Table 2.

As an example, the results for the production of silicon dioxide are presented in more detail in this section. Detailed information on the calculations and LCI results for each non-confidential substance can be provided upon request.

Highly dispersed silicon dioxide ('fumed silica') is used in the dispersion step during the galenic formulation. Here, the commercial production process for AEROSIL® by Evonik is used as a basis where silicon tetrachloride reacts with oxygen and hydrogen to silicon dioxide and hydrochloric acid (Evonik, 2020):

$$2H_2 + O_2 + SiCl_4 \rightarrow SiO_2 + 4\ HCl$$

Based on the stoichiometric coefficients and the molar mass, the amount of each substance for the production of 1000 kg silica (reference value) is determined considering a yield of 70%. The results are presented in Table 3.

The energy demand is estimated by applying the approaches described in the method section (see ch. 2.2.1). For this purpose, four sequential processes are considered by following the description by (Evonik, 2020): First, $SiCl_4$ is heated up and vaporized at 57 °C. Second, it is mixed with oxygen and hydrogen and the reaction mass is burned at 1600 °C. Third, the reaction mixture which consists of SiO_2, HCl and unreacted educts, is cooled to 190 °C. Fourth, a purification step is performed through deacidification at temperatures between 350 and 425 °C to remove HCl which adsorbed onto SiO_2 particles (Schumacher et al., 2006). Since some data such as the reactor volume or gas velocity is missing, the energy demand for the purification step is estimated by assuming that all inputs need to be heated to the maximum temperature of 425 °C in the separation column. The majority of the remaining reaction mixture, however, leave the reactor as gaseous waste stream. The overall energy demand for the production of silicon dioxide is presented in Table 4.

Other input materials are water (make-up) and sodium chloride solution (11.2%) by following the approach of Jiménez-González and Overcash (2000) for a generic cooling tower, as well as steam and air for the simplified model of the purification process based on Schumacher et al, (2006).

As described in ch. 2.2.1, outputs consist of yield losses, the by-product, waste residues due to pretreatment of cooling water, evaporated water and blowdown water from cooling tower, exhaust air and water vapor from purification as well as other fugitive emissions. These outputs are summarized in Table 5.

Average transport processes for chemicals and waste are inserted and applied to all processes where transportation activities are not included in the aggregated datasets.

All flows and unit processes for the LCI model of silicon dioxide are summarized and presented in a flow chart (see Fig. 2).

Inventory data is analogically estimated for all other materials where no unit processes exist. In the case of two materials (hypromellose and magnesium stearate), the approach by Hischier et al, (2005) is applied due to limited data availability.

Based on the aforementioned procedure, we were able to estimate inventory data for all substances for which no unit processes exist. This procedure is in alignment with current practice in the chemical and pharmaceutical sector (Parvatker and Eckelman, 2018). Most of the elementary flows in the existing model were thereby included and the complete omission of certain chemicals could be prevented. Due to a limited number of datasets in existing LCA databases and scarce details on the manufacturing routes, however, it was necessary to combine different approaches and databases to estimate LCI data which can lead to (methodological) inconsistencies within the model (e.g. use of allocation method or cut off rules).

Primary data, on the other hand, are provided for all processes within the core system (which is in alignment with the PCR for pharmaceutical products) whereby the data quality is judged to be very good in terms of completeness and representativeness.

Table 2
Unit processes which are not available in commercial LCI data bases For materials used in the API production, no further information can be provided since they are confidential. In the last column, the main references are listed which are used to identify the synthesis pathway.

Life cycle stage	Material	Reference
API production	Substrate	N/a (due to confidentiality)
	Catalyst 1	N/a (due to confidentiality)
	Catalyst 2	N/a (due to confidentiality)
	Catalyst 3	Aggregated dataset provided by BASF
Galenic formulation	Carboxymethyl starch	Hebeish and Khalil (1988); Lianbao (1992)
	Hypromellose	da Silva Júnior et al, (2017); Phadtare et al, (2014)
	Polyethylene glycol (Macrogol 4000)	Sakanoue et al. (2002)
	Polyvinylpyrrolidone (Povidone K30)	Lang et al. (1987)
	Magnesium stearate	Asgari et al. (2007)
	Silicon dioxide	Evonik (2020)

Table 3
Estimated material inputs and outputs for the production of 1000 kg silicon dioxide.

Substance	Formula	CAS Nr.	Educt/ Product	Amount [kg]
Hydrogen	H_2	1333-74-0	Educt	96
Oxygen	O_2	7782-44-7	Educt	761
Silicon tetrachloride	$SiCl_4$	10026-04-7	Educt	4040
Hydrochloric acid	HCl	7647-01-0	By-product[a]	2427
Silicon dioxide	*SiO_2*	*112945-52-5*	*Product*	*1000*

[a] Considered as waste (see ch. 2.2.1).

Table 4
Estimated energy demand to produce 1000 kg silicon dioxide.

Reaction step	Energy type	Amount [MJ]
Vaporizing	Heat	1057
Burning	Heat	8838
Cooling	Electricity	18
Heating (deacidification)	Heat	226
Transport (pumping)	Electricity	0.3

Table 5
Estimated amount of waste and emissions occurring from the production of 1000 kg silicon dioxide.

Output	Material/substance	Amount [kg]
Yield losses	Silicon tetrachloride	1131
	Oxygen	224[a]
	Hydrogen	28
Waste	Hydrochloric acid	2427
	Pretreatment waste from cooling tower ($CaCl_2$)	2
Emission to water	Blowdown water from cooling tower	19
Emissions to air	Water evaporated (from cooling tower and purification)	420
	Silicon tetrachloride (fugitive loss)	81
	Oxygen (fugitive loss)	4[a]
	Hydrogen (fugitive loss)	0.5
	Used air (from purification)	52

[a] The total amount of oxygen (yield losses and fugitive emissions) is assumed to be completely emitted to air without further treatment.

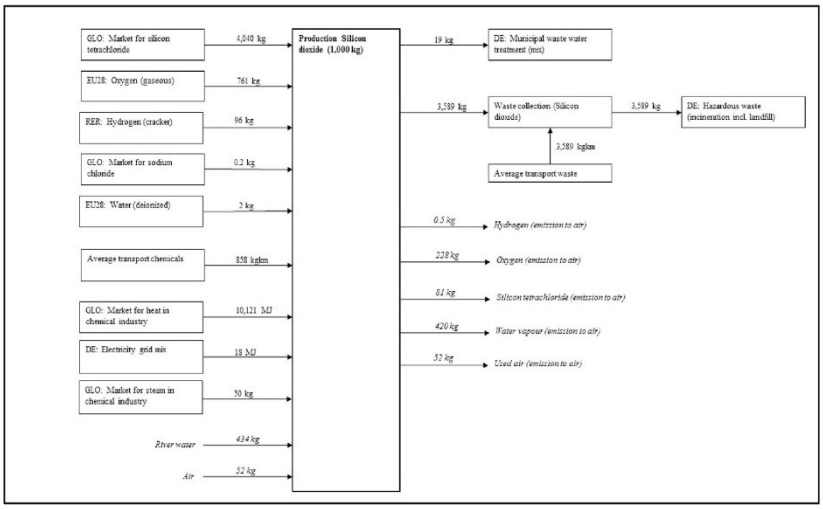

Fig. 2. System diagram for the production of silicon dioxide All flows are referred to the production of 1000 kg silicon dioxide. The bordered boxes represent aggregated datasets/unit processes while elementary flows are illustrated as italic flows.

In general, worst case scenarios and assumptions are applied here to ensure that environmental impacts are not potentially underestimated. However, many chemical manufacturing processes are optimized with regard to process efficiency such as achieving higher yields, marketing by-products, reusing auxiliary materials (such as catalyst recycling) and utilizing waste heat. Processes described in patents, however, are usually experiments on a lab scale which do not consider those optimization measures. Therefore, using upscaled data from patents can lead to an underestimation of the resource efficiency compared to full scale operating chemical plants.

3.1.2. Distribution, use and EoL

For the distribution phase, two different activities are defined: The distribution from the manufacturing plant to the pharmacy, and the transport to by the patient. The results are presented in Table 6.

The elementary flows arising from the transportation processes are allocated to the weight of the transported product which is 18.17 g total weight of one pack Eudorlin® Extra (i.e. 10 tablets, blister, secondary packaging and leaflet). For the distribution from the manufacturing plant to the pharmacy, the amount of transported good is increased by a default loss rate of 5% (referred to the reference flow) to take the quantity of unsold pharmaceuticals into account (EC, 2017). The environmental impacts related to the transportation and disposal of these unused pharmaceuticals are solely allocated to the distribution stage since product losses during the manufacturing are already included in the primary production data.

Table 6
LCI data on transportation during the distribution stage (baseline scenario).

Activity	LCI data	Reference
Distribution from manufacturing plant to pharmacy	Distance: 500 km (worst case) Vehicle: Lorry (EU-28, transport incl. fuel, Euro 0–6 mix, 22 t total weight, 17.3t max payload) Transported good: 1.05 packages Eudorlin® Extra	Primary data on transportation distance and type of vehicle provided by case study partner Aggregated transportation process (lorry) from GaBi database (Thinkstep, 2020)
Transport from pharmacy to patient	Distance: 10 km Vehicle: Passenger car (Car petrol EURO 4 (EN15804 A4)) Transported good: 1 package Eudorlin® Extra	Secondary data on transportation distance and type of vehicle by following (Siegert et al., 2019a) Aggregated transportation process (passenger car) from GaBi database (Thinkstep, 2020)

As previously described (ch. 2.2.2), emissions from the use and EoL stage consist of API emissions and non-API emissions. The latter occur from the disposal of the leaflet and packaging of the administered product which includes the transport of 12 g material (total amount of leaflet and packaging waste per reference flow) and the subsequent combustion in a municipal waste incineration plant (with thermal recovery).

API emissions, however, refer to both, the parental compound as well as metabolites. By following the procedure presented in ch. 2.2.2, the excreted amounts of each substance entering the WWTP ($API_{Influent}$) are determined (all absolute values are referred to the reference flow, i.e. 4000 mg ibuprofen): 940 mg enter the WWTP as parental compound, 1258 mg as 2-hydroxy ibuprofen and 1802 mg as carboxy ibuprofen. Subsequently, the degradation in the WWTP and emission of each substance to the environment is estimated with SimpleTreat 4.0. The results are summarized in Table 7.

These values do not represent actual concentrations which can be applied to risk assessment studies but absolute values based on a mass balance which are referred to the FU.

The calculation of the distribution of ibuprofen, 2-hydroxy ibuprofen and carboxy ibuprofen strongly depends on certain input parameters that needs to be applied to the model, such as pharmacokinetic or chemical-physical properties. This data, however, can vary significantly depending on the experimental design, and publicly available information (especially on metabolites) is very limited. For instance, only two publications could be identified that describe the biodegradation of the two main metabolites in activated sludge batch experiments (Collado et al., 2012; Ferrando-Climent et al., 2012). Half-times are used to calculate the biodegradation rate constant for each substance (see SM ch.2) which is assumed to be the most sensitive parameter in the SimpleTreat model (Lautz et al., 2017). Nevertheless, the actual amount of metabolites could be higher since they can also be formed in WWTP through the degradation process of the parental compound (Collado et al., 2012). But these interactions and transformation effects within the WWTP are not considered here. The irregular disposal of unused pharmaceuticals via sinks or toilets poses an additional risk which could lead to an increasing quantity of API that reaches the environment (Bound and Voulvoulis, 2005). On the other hand, this effect is counterbalanced by a calculated removal rate of 50% (see Table 7). This value is relatively low compared to other examples that mention removal rates up to >90% for ibuprofen (e.g. Camacho-Muñoz et al., 2012) and therefore might lead to an overestimation of API in the effluent. This is also confirmed if

Table 7
LCI data on API emissions to the environment after use $API_{Influent}$ is either biodegraded in the WWTP ($API_{Degraded}$), evaporates during the wastewater treatment ($API_{Evaporated}$), accumulates in the sewage sludge ($API_{Solid\ matter}$) or is emitted to surface water ($API_{Effluent}$). This distribution is estimated based on calculations with SimpleTreat 4.0

Substance	$API_{Influent}$ [mg]	$API_{Degraded}$ [mg]	$API_{Evaporated}$ [mg]	$API_{Solid\ matter}$ [mg]	$API_{Effluent}$ [mg]
Ibuprofen	940	445.09	0.09	15.79	479.02
2-hydroxy ibuprofen	1258	605.48	0.00	1.00	651.52
carboxy ibuprofen	1802	1143.73	0.00	2.16	656.11

the absolute value is converted into a concentration: For this purpose, the effluent concentration of 479.02 mg is divided by 1.2 m^3 water (0.3 m^3 water (sewage flow in SimpleTreat) multiplied with the treatment period of 4 days), which results in a concentration of ~399 μg/L. By applying a dilution factor of 10 (according to EMEA, 2018), a predicted environmental concentration of 39.9 μg/L for German surface water is calculated which is higher than the maximum measured concentration of 31 μg/L for ibuprofen in European water bodies (Loos et al., 2008).

Non-API emissions could be underestimated by allocating them solely to the amount of API without considering the amount of wastewater and sewage sludge occurring from this life cycle stage. However, environmental impacts related to the use of sanitary facilities are excluded since there is not yet a way to assign these effects properly to the FU for pharmaceuticals even though some approaches already exist to allocate the associated impacts to other products, e.g. to the consumption of food (Munoz et al., 2007). Nevertheless, these particular non-API emissions are deemed to be insignificant due to the relatively small quantity of pharmaceuticals that is consumed (e.g. compared to food intake).

3.2. Life cycle impact assessment

By following the procedure described in ch. 2.3, the LCIA is performed in GaBi LCA software and the contribution of each life cycle stage to the overall results is determined. Table 8 summarizes the LCIA results (absolute values) in an aggregated form for the entire product system. To reduce the influence of value choices, no weighting of the impact categories is performed.

The relative contribution of each life cycle stage to the environmental profile of Eudorlin® Extra is presented in Fig. 3.

It is obvious that the production stage is the largest contributor to all impact categories whereas the use and EoL stage seems to be negligible in this study. To further support the interpretation step and subsequent decision making, another contribution analysis is performed on a process level. For this purpose, processes are ranked based on their individual contribution to the LCIA results to determine potential environmental hotspots within the product system. They are deemed to be significant, if the sum of the processes with the highest individual contribution accounts for ≥50% of the total results in each impact category. The results are presented in Table 9. As an example, a detailed contribution analysis for the galenic formulation in the form of an environmental heat map can be found in the supplementary material (Fig. S2).

Table 8
LCIA results for Eudorlin® Extra The absolute values are presented in an aggregated form (for all life cycle stages) and all results are related to the FU. The abiotic depletion potential (elements and fossil) as well as global warming potential are calculated by using CML 2001–Jan. 2016, the ecotoxicity and human toxicity potential are assessed by applying USEtox 2.1.

Impact category	LCIA result
Abiotic depletion (ADP elements) [kg Sb-eq.]	3.45E-7
Abiotic depletion (ADP fossil) [MJ]	2.23
Global Warming (GWP) (excl. biogenic carbon) [kg CO_2-eq.]	0.145
Ecotoxicity (recommended and interim) [CTUe]	269
Human toxicity (cancer) (recommended and interim) [CTUh]	5.13E-9
Human toxicity (non-cancer) (recommended and interim) [CTUh]	1.08E-7

On a process level, the use of catalyst 2 within the production accounts for the majority of the overall results for ADP (elements). This can be traced back to the amount of the precious metal used for the catalyst preparation.

The results for ADP (fossil) and GWP are particularly related to the purchasing activities of the patient during the distribution stage, i.e. the fossil fuel consumption for the passenger car.

Surprisingly, the production of the leaflet ('paper, printed') contributes significantly to the ecotoxicity whereas the emissions of the API after the WWTP (use and EoL stage) are negligible. This could have several reasons: First, the leaflet accounts for about one third of the total mass of the final product which can correlate to the LCIA results and therefore, be one indicator for the environmental burden. Second, the aggregated dataset from the Ecoinvent database ('GLO: market for printed paper' (Wernet et al., 2016)) contains a considerable amount of aluminum emissions to fresh water ('ecoinvent long-term to fresh water') which lead to a very high ecotoxicity potential. These aluminum flows do not appear to be direct emissions from the printing process but rather background emissions from the upstream chain, e.g. the manufacturing of the printing equipment. However, it is not possible to clearly identify the origin of these emissions due to the aggregated character of the dataset. Complementary to this Gandhi and Diamond (2018), discuss the magnitude of the CFs for aluminum in USEtox which could cause a potential overestimation by applying this impact assessment method to metal flows.

The low contribution of the use and EoL stage, on the other hand, can be explained by the fact that ibuprofen is largely metabolized in the human body. Thus, the majority of emissions to the WWTP and subsequently to the environment consist of the two metabolites 2-hydroxy ibuprofen and carboxy ibuprofen (see also Table 8). For these substances, however, no CFs exist since information on their potential ecotoxicological effects are very limited. The environmental impact of these substances is therefore not reflected in the results which can lead to an underestimation of the corresponding process in the EoL stage. The problem of missing CFs also applies to other elementary flows such as the emissions of N-beta-hydroxyethylpyrrolidone (occurring from the production of vinyl pyrrolidone) and silicon tetrachloride (from production of silicon dioxide).

The human toxicity potential (cancer) is mainly due to two elementary flows to fresh water, namely polychlorinated dibenzo-p-dioxins (2,3,7,8-TCDD) and chromium. PCDD and CDD emissions can be clearly assigned to the PVC foil production whereas chromium emissions appear in numerous processes within the product system, mainly from investment goods that use steel which contains chromium. The main contributors to this impact category are chromium emissions occurring from reactant 1 (API production) and printed paper production (packaging/assembly). Nevertheless, they are most likely linked to upstream flows from basic materials such as metal production and are not specific to this product. Therefore, they must be seen in the context described by (Gandhi and Diamond, 2018).

The results for the non-cancer human toxicity potential mostly stem from mercury emissions ('heavy metals to air') due to incineration processes of hazardous waste, particularly during the production of silicon dioxide (galenic formulation). It is expected that these elementary flows do not occur from the incineration process itself since no

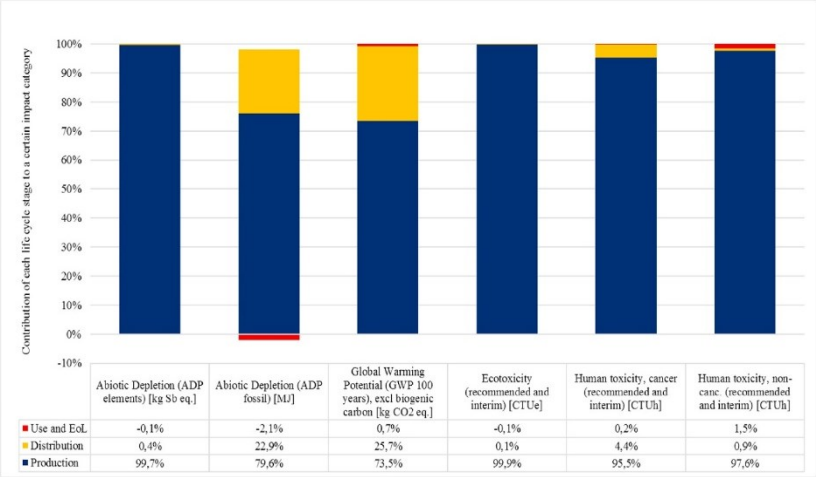

Fig. 3. LCIA results for Eudorlin® Extra The environmental profile illustrates the relative contribution of each life cycle stage to a certain impact category. The negative values occur from credits given through some processes such as the incineration of waste with thermal recovery or material recycling (e.g. metals).

Table 9
Contribution analysis and ranking on a process level The table consists of significant processes with the highest individual LCIA results and illustrates their contribution to the total results in the respective impact category.

Impact category	Contribution [%]	Process	Life cycle stage
Abiotic depletion (ADP elements)	44	Cat. 2	Production
	11	Reactant 1	Production
Abiotic depletion (ADP fossil)	22	Purchasing by patient	Distribution
	16	Substrate	Production
	10	Paper, printed	Production
	10	Steam	Production
Global Warming (GWP)	25	Purchasing by patient	Distribution
	11	Paper, printed	Production
	9	Steam	Production
	8	Substrate	Production
Ecotoxicity	42	Paper, printed	Production
	19	Reactant 1	Production
Human toxicity (cancer)	30	PVC film	Production
	21	Paper, printed	Production
Human toxicity (non-cancer)	29	Silicon dioxide	Production
	26	Haz. waste treatment	Production

mercury is applied during the production stage. As in the case of eco-toxicity, also some uncertainties exist if metals are assessed with the USEtox method (Fantke et al., 2017). This could explain the high contribution of these specific elementary flows to the ecotoxicity and human toxicity potential. These examples reveal the limits of the USEtox approach to identify more specific risks with regard to human toxicity and eco-toxicity posed by certain substances. Additional work might be beneficial to get a different view on these particular impact categories (Landsiedel and Saling, 2002). For instance, a new risk-based approach was developed by Kalberlah et al, (2019) to evaluate the toxicity of chemicals, followed by the ProScale approach (ProScale, 2017). As already described in the PCR for pharmaceutical products, ProScale provides a different perspective on the toxicological effects of product systems and instructive findings which can be complementary to the USEtox results.

To re-assess the contribution of processes within the use and EoL to the LCIA results, flows for wastewater and sewage sludge are added to the model. For this purpose, the amount of wastewater from toilet flushing (33.4 L) is obtained from Munoz et al (2007) and then allocated to the excreted amount of API (worst case: sum of parental compound and metabolites), resulting in a wastewater flow of 0.1 L. The amount of sewage sludge per liter wastewater is calculated from UBA (2019) for German conditions (approx. value: 0.6 g sewage sludge/L wastewater). By integrating these flows to the model, we increased the quantity of wastewater from 0.004 L to 0.1336 L and sewage sludge from 0.02 g to 0.1 g but the total LCIA results do not change except for the impact categories 'human toxicity, cancer' (+0.8%) and 'human toxicity, non-cancer' (+3.7%). The results confirm the assumption that these flows do not significantly contribute to the environmental profile of Eudorlin® Extra.

Even though the use and EoL stages appear to have a rather low contribution to the overall environmental impact of Eudorlin® Extra, further work is needed to enhance the availability and quality of relevant underlying data for parental compounds and their metabolites. For the calculation with SimpleTreat, for instance, some substance specific parameters such as the log Kow values for the two metabolites had to be estimated with Quantitative Structure Activity Relationship (QSAR) models. However, those calculated values may only be considered as indicative (worst case) as they often refer to the unionized form. For ionized compounds such as pharmaceuticals, the use of measured distribution coefficients might be more appropriate. Furthermore, it can be concluded that all three substances (parental compound and metabolites) are fully dissociated at environmentally relevant pH (e.g. 6–9) and thus, vapor pressure and water solubility could be higher whereas the adsorption potential is probably lower. This may lead to a higher variability of the calculated distribution pattern.

The partitioning behavior of ionized substances has been already enhanced in the updated SimpleTreat version 4.0 (Struijs, 2014), but more reliable data on chemical-physical properties is needed to generate meaningful estimations of these API emissions.

In general, it is confirmed that processes related to the manufacturing of the product contribute significantly to the LCIA results, especially compared to the distribution, use or EoL stages. This may be due to the high availability of primary data for manufacturing-related processes which provides us with a comprehensive inventory of inputs and outputs for this life cycle stage. Furthermore, the manufacturing, especially of the API production, comprises complex multi-step processes involving numerous chemicals and other input materials which can result in increased environmental impacts. This is in alignment with previous studies that describe the high environmental relevance of pharmaceutical production processes due to their resource-intensive and chemically complex nature (e.g. Wernet et al., 2010).

To further assess the sensitivity and reliability of the findings, the processes with the largest contribution to the LCIA results (according to

Table 9) are selected and additionally evaluated in a sensitivity analysis by following the procedure described in ch. 2.3. The results are illustrated in Fig. 4.

The sensitivity analysis reveals that the preparation of 'catalyst 2' and the production of 'paper, printed' are the most sensitive processes in the respective impact category.

The LCI data related to the preparation of catalyst 2 is estimated according to the general procedure described in ch. 2.2 and 3.1. Here, we assume for practical reasons that the entire catalyst consists of primary material and the catalyst recycling is not included (worst case). This can lead to higher resource consumption. In reality, however, the catalyst is recycled on a regular basis which is expected to tremendously reduce the amount of primary precious metal. This should be considered if the results are interpreted.

For the process 'paper, printed', the interpretative evaluation of the results with regard of possible value choices and assumptions remains challenging due to the aggregation of the elementary flows in this particular dataset. Since no feasible alternative dataset could be identified which include both, the paper production as well as the printing, additional interpretation steps are necessary:

The results from both, the contribution and sensitivity analyses exposed some difficulties in interpreting LCIA results if aggregated data sets from different commercial LCA databases are used and combined with primary data. It may lead to methodological inconsistencies (e.g. regarding the allocation method used) and it can also impede the interpretation of the results if no sufficient background information on the dataset is provided. From a practical point of view, however, it is nearly impossible to solely use one data source due to the general limited availability of proper data (Jiménez-González and Overcash, 2014). Besides the dataset 'paper, printed', the hazardous waste treatment during SiO_2 production ('DE: Hazardous waste' (Thinkstep, 2020)) appeared to be another aggregated process which is relevant for the validity of the LCIA results. Each of these two unit processes contains one major elementary flow that is significant for the environmental profile but cannot be directly related to the primary data: aluminum emissions to fresh water ('paper, printed') and mercury emissions to air ('hazardous waste treatment').

To examine the influence of these specific elementary flows, they are removed from the life cycle inventory.

The exclusion of aluminum emissions from the process 'paper, printed' results in a significant change of the ecotoxicological potential which is also confirmed if the unit process is completely excluded. The outcome is depicted in Fig. 5.

Obviously, the exclusion of this particular elementary flow (or the corresponding unit process) leads to a significant change of the individual contributions within the production stage: The API production and galenic formulation become more relevant for this impact category whereas the share of the packaging and assembly is the lowest compared to the two other manufacturing steps. The distribution and use and EoL stage remain negligible for this impact category.

By excluding mercury as an elementary flow from the unit process 'hazardous waste treatment', the results for the human toxicity (non-cancer) also change significantly: The contribution of the galenic formulation decreases whereas the relative contribution of the API production doubles. Since none of the waste streams during the SiO_2 production contains mercury and we applied an aggregated dataset from GaBi that represents the treatment of an average composition of hazardous waste in Germany, it is more likely that this particular flow originates from dataset-specific assumptions regarding the waste composition. This high variability of results highlights the potentially strong impact of certain aggregated datasets/flows on toxicity-related impact categories and it emphasizes the environmental importance of all three manufacturing stages.

Thus, complementary interpretation steps are essential to make LCIA results fully transparent and to avoid an underestimation of any processes or life cycle stages. Special attention shall be paid by LCA practitioners if aggregated datasets are utilized and if these processes turn out to be highly important for the environmental profile of the product system. Additionally, it could be advisable to supplement future toxicity-related impact assessment results with alternative LCIA methods such as the ProScale approach (ProScale, 2017).

4. Conclusion and outlook

A full cradle-to-grave study on Eudorlin® Extra, an ibuprofen containing analgesic, is performed to determine the environmental profile of a well-known and widely used pharmaceutical. Primary data is available for the API production, the galenic formulation and the packaging. Existing and new approaches to estimate LCI data are applied to close data gaps in the upstream (e.g. production of precursor chemicals). For this purpose, data from patents and other sources is obtained and, if necessary, upscaled to an industrial scale. Hence, LCI data for each input material that is utilized in the production process is calculated if no commercial LCI data set is available. The use and EoL stages are also considered by applying a simplified estimation model that was previously published. In contrast to the vast majority of existing LCA studies from the pharmaceutical industry, we thereby do not only focus on the manufacturing process but the entire life cycle of the product. Further methodological guidance and data sources are obtained from the PCR for pharmaceutical products and processes.

The LCIA results revealed that the production and distribution stages are factors which affects the environmental profile of Eudorlin® Extra the most. On the other hand, the use and EoL stages do not substantially contribute to the overall results. The environmental hot spot, however, depends on the impact category under study. The most sensitive processes are the production of a catalyst ('Cat.2') for the impact category

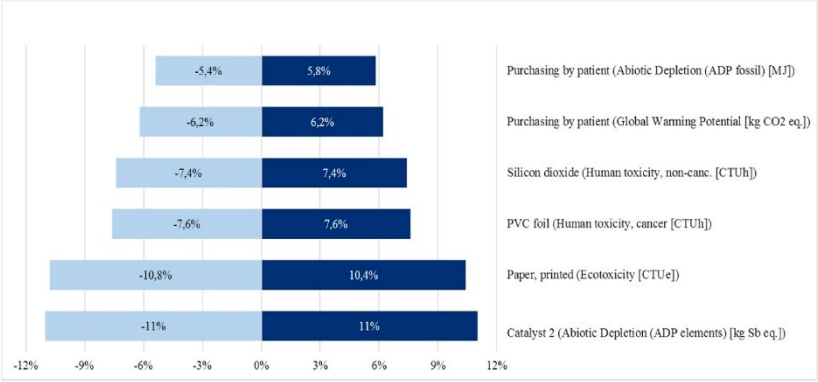

Fig. 4. Sensitivity analysis for the environmental hotspots of Eudorlin® Extra To determine the sensitivity of the most significant processes to the particular LCIA results, the values for each process and all associated upstream processes are varied by ±25%.

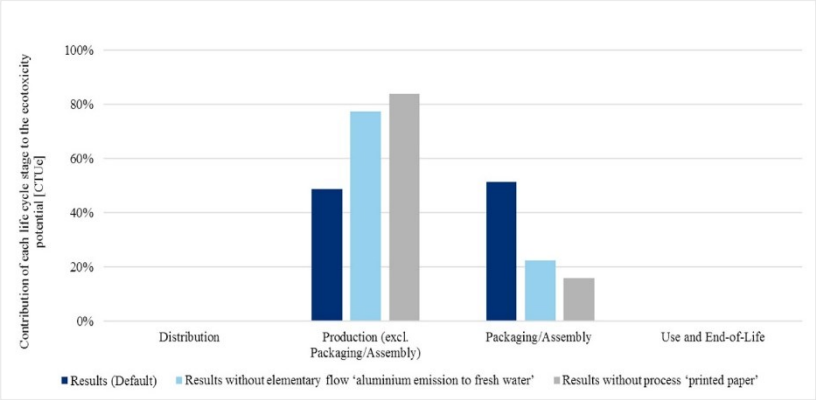

Fig. 5. Influence of the unit process 'paper, printed' on the ecotoxicity potential Relative contribution of the production stage.

'abiotic depletion (elements)' and the production of the leaflet ('paper, printed') for the impact category 'ecotoxicity'. For the latter, an aggregated dataset from Ecoinvent is utilized. However, aggregated datasets are usually modelled as a black box and therefore, it is difficult to assign an elementary flow to a certain processing step or to derive optimization measures from these data sets. Hence, these results from single processes should be interpreted with caution. Surprisingly, the emission of the API (parental compound) after the WWT do not result in an increased ecotoxicological or human toxicity potential. This is likely due to the relatively small amount of parental compound in the effluent compared to metabolites and other emissions from the life cycle. Furthermore, there are no characterization factors for the main metabolites and thus, their toxicological potential is not reflected in the LCIA results.

To overcome these obstacles and further facilitate the application of LCA in the pharmaceutical sector, we therefore propose the following measures and future research activities.

First, characterization factors for APIs as well as their (main) metabolization products should be developed and published. Additionally, existing impact assessment methods and their suitability for the assessment of these substances need to be further investigated.

Second, more comprehensive, compatible datasets should be published in commercial databases or other LCA studies (e.g. in the form of bill of materials) to make them available to other LCA practitioners and thus, to reduce the resources for individually obtaining this data. To this end, future research activities should focus on substances that are widely used in the pharmaceutical sector, such as inputs for certain galenic formulations.

Third, estimation approaches to obtain LCI data for the chemical sector need to be updated and possibly adjusted to the requirements in the fine chemical and pharmaceutical industry.

Declaration of competing interest

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

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Appendix A. Supplementary data

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4 Discussion

In the previous section, the results in the form of three publications are presented. To facilitate the consecutive discussion and to identify remaining challenges, core findings of these publications are outlined with regard to the research questions.

- *How should a LCA framework for pharmaceutical products be outlined to provide methodological guidance on sector-specific questions and challenges (RQ.1)?*

  The general concept of PCR is used as a formal blueprint for the framework development. Generic LCA documents, sector-specific guidelines, existing PCRs and LCA case studies are utilized as a structural and content-related basis. The strong relatedness particular to the (fine) chemical sector, however, impedes a strict separation of these product categories: Especially for LCA case studies of pharmaceutical intermediates, it is difficult to decide whether they belong to the pharmaceutical or (fine) chemical sector. This circumstance makes it even more challenging to identify and compare proper studies that are useful for the framework development.

  Based on this bottom-up approach, formal and content-related requirements are composed and depicted for selected examples (i.e. specification of product category to ensure comparability, definition of product system and system boundaries, functional unit, use- and EoL stage, additional information and other cross-cutting issues) where pharma-specific rules are deemed to be necessary. First fundamental methodological specifications are provided for future LCA studies from the pharmaceutical sector. Due to the complexity and versatility of the topic and formal requirements of the journal, some issues such as spatial aspects, the influence of the galenic formulation, or modelling the use and EoL stage are only touched upon in the first paper superficially. They are either addressed in other publications or further explained and integrated in the PCR for pharmaceutical products and processes (Siegert et al. 2019a). Finally, the framework is applied in a case study presented in the third publication, whereas a systematic, comprehensive field-test of the framework's practicability and transferability to other product group is not part of the publication.

- *How can life cycle stages beyond the manufacturing stage of pharmaceuticals be modeled (RQ.2)?*

  Initial thoughts about a qualitative concept to model the use and EoL stage of a pharmaceutical are already presented in the first publication. But since this has been identified as one major gap in the application of LCA in the pharmaceutical sector, the concept is refined and a more detailed inventory model for the use and EoL stage is outlined in the second publication. For this purpose, the respective processes and flows are depicted depending on the different

galenic formulations, and calculation approaches as well as respective data sources for each flow are presented. To achieve the goal of an easy-to-use approach to model the use and EoL stage, a limitation of the geographic scope as well as modelling assumptions are inevitable. For instance, we only consider German conditions which implies certain standards regarding WWT and waste management. Furthermore, other simplifications such as the neglection of transformation products outside the body (e.g. due to bacterial degradation within the WWTP) are made, primarily due to a challenging data basis. The model has been tested for one example (oral intake of 1 tablet ibuprofen) but it´s application needs to be further evaluated and validated for other galenic formulations/types of medicine.

Other life cycle stages beyond or processes within the manufacturing stage, such as pre-manufacturing processes/research and development (R&D), are not yet considered in the framework.

Due to the complementary character of all three publications, the discussion section is divided into methodological (chapter 4.1) and practical (chapter 4.2) challenges related to the overall results presented in chapter 3. To this end, a critical appraisal of the research is examined complementing and broadening the discussion within the publications. In addition, novel findings of this work are put in the context of the current scientific state of the art.

4.1 Methodological challenges

This chapter further addresses remaining methodological challenges and open issues arising from this research. Furthermore, it presents potential approaches to overcome these obstacles.

4.1.1 Underlying literature update and comparison with the current framework

According to ISO 14025 chapter 6.7.1 (ISO 2006a) and ISO/TS 14027 chapter 6.1 (ISO 2017), a PCR shall be based on relevant LCA- and/or footprint studies or other environmental information. Thus, the framework complies with these criteria for PCR development and harmonization with regard to its structure and content by building upon existing standards, sector-specific guidelines, PCRs and pharma-LCAs but the content goes beyond existing PCRs. For instance, it follows the modular approach for Type III Environmental Product Declarations but further specifies the product system by redefining the life cycle modules for pharmaceuticals. Thus, respective processes can be clearly assigned to the upstream, core and downstream system which is crucial since this is contingent on data quality requirements (especially in the case of generic pharmaceuticals with complex supply-chains through sub suppliers and other service providers).

To ensure the currency of the framework, an update of the underlying literature research according to the first publication is performed. As already mentioned in chapter 3.1, it results in 7 new pharma-LCAs (Jung et al. 2021; Marco et al. 2019; Parvatker et al. 2019; Renteria Gamiz et al. 2019; Sharma et al. 2020; Wang et al. 2021; Yang et al. 2021) and one new sector specific guideline (Pålsson et al. 2019). Searching the databases of existing program operators compiled by Minkov (2020) results in neither PCR nor EPD for pharmaceuticals or related product categories.

All LCA case studies assess a product system from cradle to gate focusing on the manufacturing process, with the exception of (Jung et al. 2021) who evaluate different galenic formulations from a cradle to grave perspective. Hence, the current tendency within the sector to examine pharmaceutical manufacturing processes rather than applying LCA to pharmaceutical products is confirmed. It is noteworthy that two case studies (Jung et al. 2021; Yang et al. 2021) are already referring to the framework and applied some methodological requirements in their work. However, significant deviations or novel aspects which should be integrated in the current framework could not be identified within the case studies. In general, the supporting (or underlying) LCA or footprint studies revealed a particular benefit to collect information on common practice with regard to the goal/intended application of the study, the FU definition, impact assessment categories and methods as well as potential data sources. But their actual use to derive rules within the framework development is limited due to their restricted scope and methodological variabilities. A broader focus

on other LCA studies, e.g. related to chemicals and WWT methods, could probably gain further insights into life cycle sections.

A publication by the IVL Swedish Environmental Research Institute reveals a high pertinence for this work. The authors outline a two-dimensional environmental assessment model for pharmaceutical products including (1) API emissions from a risk assessment perspective and (2) a product carbon footprint based on the product life cycle. Furthermore, they present a PCR draft ('PCR embryo') on pharmaceutical products to enable comparison of pharmaceuticals with the same API and, in the long-term, increase the quality and reliability of LCA results. Within their proposal, they exclude communication purposes and environmental impact categories other than climate change.

Since the current framework presented in this thesis is based on the LCA methodology, particular attention is paid to the carbon footprint and PCR development presented therein. In the following, similarities and deviations are shortly described:

Within their work, they confirm the use of ISO 14025 (and explicitly PCR) as well as other sources which have been already incorporated in the framework development (e.g. the 'Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices' from the National Health Service (NHS 2012)) as a groundwork for a life cycle-based evaluation of pharmaceutical products.
They also emphasize the use of generic and more specific rules ('level of reporting') which is common practice for EPD programs or other initiatives such as PEF. With regard to a product category definition, the authors refer to the proposal herein which utilizes the ATC classification system but they also stress the complexity to define appropriate product categories based on the individual function of a pharmaceutical (see also chapter 4.1.2).
More generic rules such as allocation procedures and data quality requirements are identical and follow the requirements according to ISO 14040/44.

Slight differences can be found in the definition of the product system, i.e. life cycle stages and modules. For simplicity reasons they solely focus on API production and galenic formulation within the PCR embryo. Even though the authors are aware that different manufacturing steps can be performed by multiple suppliers and thus, different data quality requirements apply (e.g. the demand for site-specific data), they only differentiate between 'cradle to gate API', 'cradle to gate pharmaceutical product' and 'cradle to grave pharmaceutical product'. This, however, does not include the case that, within the manufacturing stage, the API synthesis, the galenic formulation and the packaging can be carried out by three different companies.
Although a broad consensus exists with regard to the inclusion/exclusion of (non-)attributable processes, there are some deviations, especially regarding the use and EoL stage: Contrary to the

framework presented herein, the PCR embryo generally excludes processes related to equipment to administer the pharmaceutical product, human metabolism, or effects of the pharmaceutical after entering the environment.

Another controversial point of discussion is the definition of the FU. Here, the authors propose either a mass-based FU for 'cradle to gate API' studies which is in alignment with the framework. For other scopes (i.e. 'cradle to gate pharmaceutical product' and 'cradle to grave pharmaceutical product') they propose a FU of 1 Defined Daily Dose (DDD), whereas an effect-based FU (as proposed in the framework) would lead to an increase of results that need to be reported for a product (depending on the treatment scenario). This is a valid argument since it increases the degree of complexity in a study. However, the definition of a FU is strongly related to the product category definition and thus, pivotal for the comparability of products: According to ISO 14025, a product category is 'a group of products that can fulfill equivalent functions' and a FU is the 'quantified performance of a product system for use as a reference unit'. ISO/TS 14027 further specify the FU as 'the intended function or service of the product'. Hence, the same FU shall be applied within one product category. Comparability is only given if products belong to one product category, i.e. fulfill a equivalent function (expressed by the FU). The DDD, however, is similarly to 1 kg API only a mass-based FU (i.e. 'declared unit') and an added value is therefore questionable. The intended function of the product is the therapeutic purpose of a pharmaceutical which should be also reflected in the FU. Reasons for the need of additional information within the effect-based FU (such as specification of the geographic region) is already described in the first publication (Siegert et al. 2019b).

Finally, the PCR embryo includes only one impact category, namely climate change. This results not only in more streamlined (single-issue) LCAs, it has also influence on other methodological choices. For instance, a mass-based cut-off criterion (possible exclusion of inputs from that contribute less than 1% to the unpackaged weight of the product) is established which might be feasible for carbon footprint studies. If toxicity-related impact categories are considered, however, a cut-off criterion based on environmental significance appears to be more appropriate since also chemical substances with a small share of weight can be highly toxic.

In summary, the trend to perform LCAs for pharmaceutical manufacturing processes rather than for pharmaceutical products is confirmed. Only few LCA case studies have been published so far with the number of LCA studies on APIs or actual pharmaceutical products being even smaller. The only PCR on vaccines for human or veterinary medicine by the International EPD system expired in 2018 without reactivation. Since then, one sector-specific guideline in form of a PCR embryo has been published. Besides many similarities, some deviations between the PCR embryo and the framework within this thesis exist which can be mainly traced back to different objectives and scopes.

4.1.2 Comparability of pharmaceuticals

Comparisons can be basically performed for either manufacturing process variants or on a product level (e.g. comparison of drugs with same API but different galenic formulations, drugs with different API and same galenic formulations but identical therapeutic application etc.). In this chapter, I solely focus on the comparability of products since manufacturing processes are an integral part of the product level. Moreover, the comparison of manufacturing alternatives is already common practice in the pharmaceutical sector, whereas the comparison of pharmaceutical products is not yet widely practiced.

One important application of PCR and EPD is to facilitate a comparison of product variants within the same product category. ISO/TS 14027 chapter 5.3 describes that ’PCR are intended to increase, as far as possible, the comparability of Type III environmental declaration and footprint communications for products in the same product category using the same PCR’. The current framework further specifies the requirements for comparability as defined in ISO 14025 chapter 6.7.2 for pharmaceutical products and thus, theoretically enables a comparison of pharmaceuticals according to the normative requirements. However, this is not current practice in pharma-LCAs which can have several reasons. A work by Soete et al. (2017) confirms that most of the manufacturing companies apply LCA for internal hot spot analyses or compare different manufacturing techniques by using a mass-based FU. Communication purposes (business to business B2B or business to consumer B2C) play a minor role. Moreover, the majority of actors from the healthcare (including pharmaceutical) sector prefer a product-specific assessment approach rather than sector- or product group-specific concept. On the downside, the need for harmonization (especially regarding LCIA) is shown, which might be contradictory to the individual product-specific perspective of some industrial parties.

Two main aspects shall be contemplated when the comparability of products is discussed: The definition of the product group (including classification) and the FU. These methodological requirements demarcate the product (group) by a function-based boundary.

The U.S. Food and Drug Administration (FDA) defines the pharmaceutical product and their function as substances ’intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body of man or other animals’ (FDA 2021) which is also in alignment with the definition by the European Commission for medicinal products (European Union 2001). This is indeed too generic for determining a proper product category that allows comparisons and thus, needs to be further specified. This is done by applying the ATC-classification scheme which allows to categorize APIs according to their chemical, pharmacological and therapeutic characteristics (see chapter 3.1). Another promising categorization scheme is published by the European Pharmaceutical Market Research Association (EphMRA). In

contrast to the ATC classification scheme, it classifies products (not substances) on three to four levels mainly according to their use and indications. Both classification systems strive for a higher convergence with a harmonization on the third classification level (EphMRA 2021). Thus, it could be used as an additional confirmatory standard within the existing approach.

It must be noted that the definition of product categories is always a compromise that comes along with simplifications regarding certain product characteristics (such as flavor, tolerability, side effects etc.). A product category should always be as accurately as necessary and as generic as possible. The decisive factor, however, is the intended core function of the product. Product sub-group definitions based on the third level of both classification schemes fulfill these requirements by premising on a widely accepted basis to cluster pharmaceutical products based on their equivalent (therapeutic) function. Multiple pharmacological functions of a drug are also covered by this approach since one API or product can be assigned to various subcategories. Within the goal and scope phase it must be determined by the developer of the study. By referring to the specific subcategory or classification code, the function of the product system under study can be unambiguously identified.

This shall be also reflected in the FU which is the quantified performance of a product system that serves as reference unit in LCA. Thus, the function (i.e. therapeutic purpose) shall be derived from the products categorization and embedded in the FU. There might be the case that multiple pharmacological effects are desired by the patient, which can be either achieved with one or several products. This needs then to be included in the FU. If only one pharmacological application is desired, however, these multiple effects should not be included since the FU only represents the ’intended ’ function (see ISO/TS 14027, chapter 6.5.2) and not unintended effects. This issue is further addressed in chapter 4.1.3.

Obviously, the definition of product categories and FU in the context of pharmaceuticals is a challenging but crucial task. By keeping the big picture in mind, it is highly recommended to include a consumer perspective more strongly (in addition to the findings by Soete et al. (2017) in future strategies to avoid misleading conclusions. There might be many cases where APIs/pharmaceuticals are highly specialized and crucial for a patient’s treatment. But these products are not the cases that are considered here. A comparison could particularly be interesting for the generic market where the consumer can actively decide which product they want to buy (given that the products are exchangeable from a pharmacological point of view). This potential for purchasing decisions is already outlined through a representative poll for the U.S. market (Dohle et al. 2013).

Furthermore, it should be noted that potential uncertainties regarding the comparability of pharmaceuticals not only arise from the definition of the product category and its function but also from the ’receiver side’: In this framework, an average patient is assumed without considering individual characteristics such as age, pre-existing conditions etc. which can also lead to significant

differences under real life conditions. However, LCA is a model-based assessment method and these generalizations are necessary boundary conditions which are already applied in other contexts, e.g. to define a DDD.

4.1.3 Positive impacts of pharmaceuticals

To provide a holistic and comprehensive basis for decision making, positive impacts of pharmaceuticals should also be taken into account to complement results from LCA studies. A benefit-risk assessment is already part within the approval process for pharmaceuticals and includes health-related as well as environmental risks. Moreover, the pharmacovigilance after market approval mainly aims at monitoring health-related risks but partly includes environmental aspects as well (at least for veterinary medicine).

LCA is a damage-oriented assessment method although some concepts have been already developed in the meantime to include positive impacts into LCA. Several studies deal with this issue (e.g. Di Cesare et al. (2018); Ekener-Petersen and Moberg (2013); Petti et al. (2018)) whereby significant overlaps to other disciplines such as Economics, Social LCA (SLCA), consequential LCA and Sustainability Assessment can be observed.

In this section, potential approaches are briefly outlined and it is described how this dimension can be integrated in the existing framework. To this end, it is necessary to differentiate between intended and not intended positive impacts. In the current framework, only the intended positive impact of pharmaceuticals, represented by its therapeutical function, is covered by implementing it into the FU (see also chapters 4.1.1 and 4.1.2). The function can be also described in the additional information if an EPD is created. According to Schaubroeck and Benetto (2018), this is one way to consider positive impacts in terms of a product´s function. However, it is questionable whether the benefits of pharmaceuticals are sufficiently included.

Within SLCA, for instance, several indicators related to the impact category ’Human health’ exist, such as ’DALY (Disability-adjusted Life Years)’, ’LEX (Life Expectance at Birth’ or ’infant mortality’ (Arvidsson et al. 2018).

DALY is one of the most prominent indicators which was developed by the World Health Organization (WHO) as an indicator that ’represents the loss of the equivalent of one year of full health’ (WHO 2021c). Thus, its use appears to be quite appropriate for pharmaceutical products which have the purpose to restore or ensure the health of a human being.

DALY is calculated as the sum of ’years of life lost (YLL)’ and ’years of life disabled (YLD)’ which include factors, such as the difference of actual age at death and life expectancy of the population, duration of disability and a severity factor from complete health to complete disability (Scanlon et al. 2013). It is already implemented as an aggregated endpoint result in the ReCiPe impact assessment method (Huijbregts et al. 2017) and can be applied to assess both, environmental impacts occurring from a

products life cycle as well as avoided impacts from the products use. Six case studies from the pharmaceutical sector already applied ReCiPe at an endpoint level calculating a DALY for the emissions of their product system from cradle to gate. The application of DALY to assess the positive impact of pharmaceuticals on human health, however, seem to be less common in the pharmaceutical industry.

The positive counterpart of DALY is the indicator QALY (’Quality-Adjusted Life Years’) as part of HALY (’Health-Adjusted Life Years’) which originates from Health Economics and represents the years of life without health-related disabilities (Prieto and Sacristán 2003).

(Debaveye et al. 2016) propose an integrated approach to reflect human health effects (benefits and burdens) of a pharmaceutical treatment. They emphasize the need of a harmonization of DALY and QALY to a single score but also underline the methodological challenges, such as quantification of reference health states, efficiency- versus equity-based weighting of ages, differences in the perspectives/meaning of both indicators, high uncertainties in predicting (in-) direct future costs and benefits and value choice perspectives within existing endpoint-based LCIA methods.

These challenges underscore the (partly) subjective character of endpoint-based LCIA and the challenging tasks to reproduce and quantify reliable cause-effect chains. This is even more uncertain if unintended positive impacts are assessed.

In a follow-up publication, (Debaveye et al. 2019) assess potential environmental benefits and burdens related to the treatment of schizophrenia by combining a Markov Model with LCA. The results are DALY (burdens) and DALY avoided (benefits) which are confirmed by separate QALY calculation. This differs from their previous approach to create a single score indicator from QALY and DALY.

Given the fact that there is not yet a clear consensus how positive impacts (of pharmaceuticals) shall be included or a harmonization of DALY and QALY to a single score can be realized, a consideration of the intended therapeutic function by means of the FU appears to be the most convenient solution. However, DALY could be used as an additional cumulative (screening) indicator (especially in the early stages of product development) to estimate which risks along the life cycle (positive DALY value) could outweigh the therapeutic purpose of the pharmaceutical (negative DALY value) and thus, to identify neuralgic points within the life cycle that need to be optimized. To this end, API emissions as part of the LCI shall also be integrated into the DALY quantification by feeding into the preceding midpoint categories. Representative scenarios with and without treatment of a patient with a pharmaceutical need to be developed to facilitate a delta analysis of the DALY for each scope. The framework published by Debaveye et al. (2019) provides a good starting point for this purpose.

However, uncertainties related to e.g. value choices remain and results shall be therefore carefully reconsidered.

4.1.4 Expansion of system boundaries

In this work, life cycle stages beyond manufacturing are limited to the use and EoL stage (see chapter 3.2) as of yet since this can be clearly assigned to a pharmaceutical product. However, some publications propose to extend the system boundaries to both directions, the upstream as well as the downstream.

With regard to the upstream, especially the inclusion of Research and Development (R&D) could be relevant for the environmental assessment of a pharmaceutical. Here, R&D includes all (non-) clinical, regulatory and post-marketing activities, i.e. processes related to the medicines´ discovery, examination, approval and monitoring after approval. This is illustrated in Figure 3.

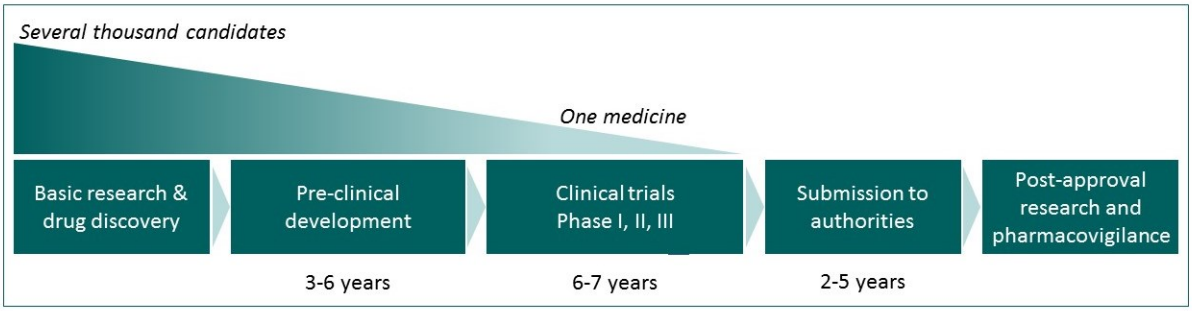

Figure 3: Generic R&D process of an pharmaceutical product according to Eupati (2021). Starting with several thousand potential candidates for certain health-related problem, it is narrowed to one single medicine for the clinical trials which needs to be finally approved.

Even though there are multiple studies in the context of R&D and LCA, however, they often discuss the role of LCA within R&D to facilitate decision making in early product development stages (e.g. Baldassarri et al. (2016); Hesser et al. (2017)). A methodological proposal how R&D can be integrated in an LCA for already developed and sold pharmaceutical products is missing.

This life cycle section is highly driven by efficiency, potential prospects of success and the actual health improvements. Thus, it is usually characterized by long-term and cost-intensive processes which can have a strong influence on the future environmental performance of the final product. Whereas some perpetual R&D activities (e.g. as part of pharmacovigilance) can be clearly assigned to the product under study, it is still challenging how (often lengthy and rarely straight) drug discovery processes in very early stages can be allocated to a single product. Contrary to other 'multi-purpose plants' where similar allocation problems occur, the output of R&D facilities is often not clearly defined and hence, elementary flows cannot be properly allocated. Furthermore, the data collection could be very challenging for research projects. This is also aggravated by current R&D strategies of pharmaceutical companies, such as outsourcing and establishing R&D cooperations etc. (Banerjee and Siebert 2017; Teramae et al. 2020). Thus, they are usually excluded in LCA studies.

Due to these challenges, it is therefore proposed to follow the ISO 14040/44 standards by avoiding allocation problems through system expansion. To this end, at least all potential environmental impacts associated with the processes after drug discovery and non-clinical development (see Figure 3) should be considered within the LCA study since the total amount of 'by-products' from the R&D process is then boiled down to only few promising candidates. Hence, it might be easier to assign inputs and outputs from subsequent processes to the final product. As we focus on already authorized products and their preceding R&D, market approval can be seen as a precondition for including R&D in pharma-LCA.

In the (expected) rare case that R&D activities cannot be clearly assigned to a single product, the R&D stage could be either separately evaluated on a qualitative or (semi-) quantitative level without considering the results in the overall LCIA (e.g. as proposed by Schimpf and Binzer (2012), or allocation could be performed. According to ISO 14044, inputs and outputs should be 'allocated between the products and functions in a way that reflects other relationships between them' (ISO 2006c). Therefore, alternatively or complementary to existing allocation methods (physical relationship or economic value), allocation could also be conducted based on the actual benefit (according to the definition within the benefit-risk assessment, BRA) of a pharmaceutical which is deemed to be the final desired result of an R&D process. For instance, (Curtin and Schulz 2011) mention the ratio of the 'Number needed to harm (NNH)' and the 'Number needed to treat (NNT)'as potential indicator to express a pharmaceutical´s BRA in clinical trials. If NNH/NNT >1, less 'patients need to be treated to observe a benefit from the drug than to have one additional occurrence of an adverse drug reactions' (Curtin and Schulz 2011). To appreciate a products´ (functional) benefit also from an environmental point of view and to promote the efficiency of R&D activities, a better BRA should result in less environmental burden compared to products with a poorer BRA. To reflect these correlations, a potential allocation factor could be calculated with the following equation:

$$Allocation\ Factor = 1 - \frac{\left(\frac{NNH}{NNT}\right)_a}{\sum_{i\geq 1}\left(\frac{NNH}{NNT}\right)_i}\ mit\ a \in i \qquad \text{(Eq.1)}$$

with the NNH/NNT ratio for an arbitrary product a (a=1,2,3,…n) and the sum of all NNH/NNT ratios for all products (including product a) that need to be considered in the allocation step. By multiplying the in-/outputs with the product-specific allocation factor, the flows can be partitioned between the desired product and the other products.

With regard to the downstream, other elements of a healthcare pathway (such as doctors' consultation, surgeries etc.) could be included. This assessment of the entire treatment pathway is already proposed in some publications (e.g. Kløverpris (2018); NHS (2015); Soete et al. (2017)) to

facilitate a fair comparison on a patient level. This might be theoretically feasible for the scope proposed by the authors, however, it also reveals some obstacles. First, this approach will most likely diminish the share of pharmaceuticals in the total LCIA results and, depending on the impact category, might distract from the environmental relevance of this product category. For example, the Global Warming Potential (GWP) (relative contribution) of the veterinary medicine IMPROVAC® is extremely low for the manufacturing step if the subsequent animal breeding and slaughter is included (Pfizer 2012). The same effect is expected if energy-intensive processes such as surgeries are involved. Second, it will increase the uncertainty of the results and effort to collect data since more inventory data, scenarios and assumptions are involved. This seems to contradict the call for simplification of the LCA method and the development of streamlined tools. Therefore, the current practice should be rather extended by a product-perspective (e.g. though a proper definition of the FU (based on the therapeutic effect) as well as the system boundaries) before assessing the complete healthcare pathway. This appears to be the more reliable way to assess the potential environmental impacts of pharmaceuticals.

4.1.5 Transferability of the framework to veterinary medicine

The current work refers to pharmaceuticals for human use. However, the findings might also be applicable to other product categories. The most obvious are certainly veterinary medicinal products, but also personal care products, dietary supplements and other goods related to the healthcare sector, such as medical devices, could benefit from the work presented herein.

Veterinary medicine, however, is of particular interest from an environmental point of view because of a high risk of direct and indirect API emissions from livestock to aquatic and terrestrial ecosystems and an affiliated threat of antimicrobial resistance due to the use of antibiotics (Beek et al. 2016). Consequently, there is a high chance for human beings to be exposed to resistant germs because of the numerous potential pathways (e.g. soil-human, soil-crop-animal-human, soil-water-human, animal-human). Finally, environmental aspects for animal drugs carry a great deal of weight since a refusal of approval due to the ERA results is theoretically possible for veterinary pharmaceuticals which is contrary to pharmaceuticals for human use (Ågerstrand et al. 2015).

Most aspects of the framework are expected to be also applicable for veterinary due to the similarities between the two product categories. This linkage between these product categories becomes also apparent by taking a look at the only (and now expired) PCR which refers to human and veterinary pharmaceutical products (IES 2014). However, some modifications might be necessary:

1) For the definition of the product category/product classification, the general framework rules can be adopted but the ATC classification scheme needs to be replaced by its veterinary counterpart ATCvet which uses the same methodological principles (WHO 2021a). For the ATCvet system, it might be sufficient to utilize the second classification level (therapeutic main group) to define the product sub-categories instead of the third level as proposed for the ATC classification scheme.

2) The FU has to be modified with regard to the ’patient’ and the disease/indication (based on ATCvet).

3) The use and EoL stages are clearly the most product group specific elements. Similar to pharmaceuticals for human use, the general procedure of intake, excretion and emission apply and veterinary medicine can be either directly or indirectly emitted to the environment. But in contrast to the application in/on humans, the ways of emissions are not only affected by different galenic formulations, but also by the form of animal husbandry (intensive/extensive), type of animal (pet/livestock) and the animal species itself. For instance, the EoL flow of liquid excrements to WWTP applies to intensive livestock breeding at most whereas this flow might be negligible for other cases which are dominated by more diffuse emission sources (Kaczala and Blum 2016). Same applies to solid and semi-solid excrements (manure/slurry) which are either directly applied to soil as fertilizer, or

collected, pre-treated and used in biogas plants. In the latter case, the product system shall contain all related treatment processes until the flow meets the end-of-waste status. Irregular drug disposal via sinks or toilets as one emission source of APIs according to Siegert et al. (2020a) is assumed to be insignificant for veterinary medicine.

4) The choice of impact categories is closely related to the definition of the product system and in particular the use and EoL stage. For instance, depending on whether or not the breeding is included in the assessment, it might be necessary to expand the existing set of impact categories since LCA studies on animal farming often include the impact categories 'acidification', 'eutrophication' and/or 'land use' (e.g. Dourmad et al. (2014); Haas et al. (2001); McAuliffe et al. (2016); OGINO et al. (2007)). As proposed in the framework, pharma-specific impacts shall also be included (either within the impact assessment or as additional information).

Conclusively, the adjustment requirements are only minor and thus, the framework should be easily adaptable for veterinary medicine. Vice versa, LCA studies on veterinary medicine could also provide valuable information on methodological issues, such as estimation approaches for missing inventory data. Therefore, they should not be completely omitted in future considerations.

4.1.6 Definition of the use and EoL stage

The description of the use and EoL stage is based on existing literature and expert knowledge. It represents the generic flow and emission of an API and further specifies these flows and emissions depending on the galenic formulation (see O.2.1). The aspiration of this objective was to provide a rather comprehensive overview of all potential API flows and emissions, i.e. the product system was not limited or restricted through a preceding selection of flows/emissions based on their (presumed) environmental significance. Moreover, it was also the basis for the quantitative use and EoL model.

However, the assignment of certain flows to specific life cycle modules may differ and was adjusted for this work: Contrary to the proposal within the first publication, transportation and distribution processes from manufacturing sites to pharmacies and hospitals as well as patient travel are not part of the use stage but included in a separate 'distribution stage' (see (Siegert et al. 2019a). Therefore, the definition of the product system has been further harmonized with the modular approach that is used by PEF and other program operators.

Yet, the attribution of some flows and processes might not be explicit (e.g. for excretion process) since they act as transition processes between the use and EoL stage which convert the product flow to a waste flow or emission. The attribution of processes and flows to a life cycle module, however, can have influence on methodological specifications, such as data requirements (see chapter 4.1.1). In this context, it is important to critically reflect at which point the product loses its product properties. For instance, what if the API is still existing in its parental form and active after excretion (i.e. might have an (unintended) pharmacological effect), and would it be still possible to (theoretically) fulfill the function according to the FU?

In this work, it was considered that a pharmaceutical can fulfill its defined function only if the API is delivered in a certain galenic formulation since it not merely determines the form of administration but has also significant effects on pharmacokinetic properties (such as absorption). Consequently, the excreted API is then no longer available for its intended therapeutic purpose and becomes a waste flow. This example illustrates why it is imperative to unambiguously define the product (including components) and its function (i.e. FU) for the subsequent modelling.

Finally, the definition of the use and EoL stage strongly depends on the geographic scope. In the second publication, German conditions are used as an example. However, some country-/region-specific adjustment might be necessary (see Figure 4).

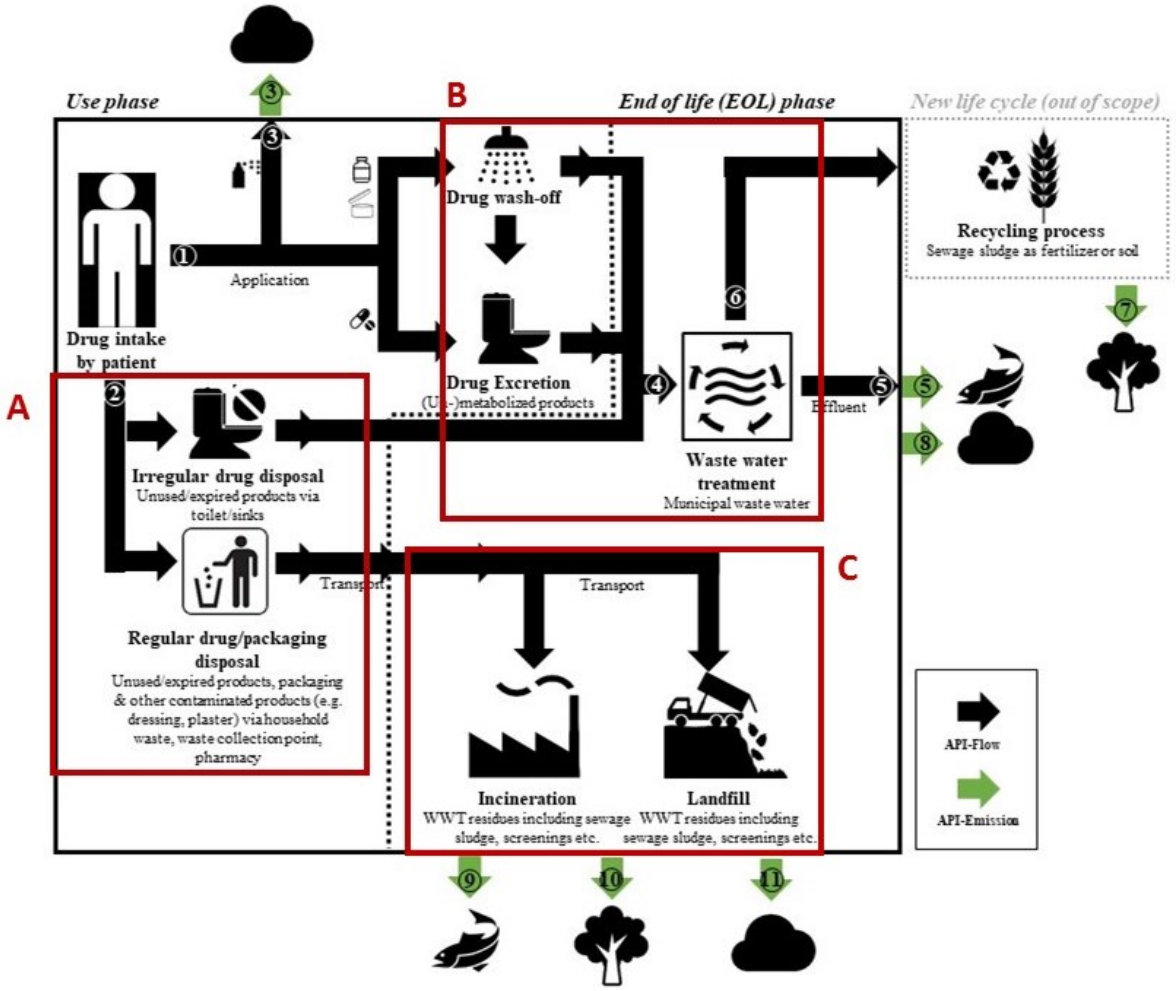

Figure 4: Influence of the geographic scope on the qualitative use and EoL model

Three main sections have been identified which are assumed to be strongly affected by the geographic scope: Disposal options and behavior of the patient (A), WWTP for grey and black water (B) and waste management (C).

A.) Significant geographic differences exist with regard to discarding options for unused/expired pharmaceuticals (even within Germany, no consistent regulation on the disposal of pharmaceuticals exists among the federal states). For example, some countries provide public take back schemes for unused or expired pharmaceuticals instead of (or in addition to) the disposal via residual waste. This can affect the disposal behavior of the patient (e.g. separation of packaging and irregular disposal rate) as well as the subsequent treatment of the waste stream.

B.) The emission pathways (via wash off and excretion) are expected to be independent of the geographic scope, whereas considerable regional differences in the presence and technology of WWTP exist. This includes not only municipal WWTP before discharge to a water body but also potential pre-treatment measures at the 'point of emission' (PoE), such as hospitals or nursing homes.

C.) Similar to the WWT technology (see B), waste management practices significantly differ among regions/countries. In Germany, for instance, the disposal pathway for pharmaceuticals via landfill is deemed to be negligible due to legislative obligations (Siegert et al. 2020a). In other (particular low-income) countries, however, landfill or open dumps without proper leachate management are still the most common method to dispose healthcare waste (Ferronato and Torretta 2019).

Due to these immense regional differences and their effect on the LCI (i.e. API emission), particular attention should be paid to these three sections. The product system should be representative for the geographic scope and (if necessary) carefully adjusted.

4.1.7 Reliability of the quantitative use and EoL model

To reduce the subjectivity from the beginning, the 'Guideline on the environmental risk assessment of medicinal products for human use' published by the EMA (EMA 2018) was applied as a basis for the use and EoL model development (see chapter 3.2) since ERA (as part of the approval procedure for pharmaceuticals) is the pivotal tool to quantify pharmaceutical emissions.

By combining LCA with Environmental Risk Assessment, a strict end-of-pipe emission-based approach is expanded by a holistic life cycle perspective. A similar approach has been followed by Pålsson et al. (2019) although their goal was to extend the current country-specific ERA framework FASS (which includes API emissions in Swedish water bodies from patients) by considering API emissions during manufacturing rather than enhancing the LCA methodology as such.

Here, in contrast, the calculation of PEC for surface water (PEC_{SW} according to phase 2 Tier B) has been taken from the ERA methodology (EMA 2018) and was utilized as a blueprint for the use and EoL model. In doing so, the equation for PEC_{SW} is adjusted for its application in LCA (see (Siegert et al. 2020a), specified for three different galenic formulations and complemented by missing content, such as pharmacokinetic information[2] and amounts of unused and disposed pharmaceuticals. Moreover, waste management and WWTP calculations are added to the model to finally estimate the API emissions (=elementary flows) to the different environmental compartments. Thus, the use and EoL model consists of two main elements that mostly determine the inventory results:

<u>1) Intake and pharmacokinetic behavior in the human body</u>

The calculation approach is based on (Ortiz de García et al. 2013) and extended for the three most important application forms.

Two fundamental assumptions have been made for the calculation: First, a steady state model is used, i.e. temporal aspects of the pharmacokinetic behavior (such as accumulation in the body) and emission are not covered. This conservative approach is common practice in (non-dynamic) LCA but also leads to potential uncertainties on LCI and LCIA results (Lueddeckens et al. 2020). Second, the conservation of mass (i.e. $m_{API(in)} = m_{API(out)}$) is the basic underlying principle applied as the body is treated as a (partial) black box.

The mass flow $m_{API(in)}$ consists of parental compound, whereas $m_{API(out)}$ can be a matrix of different substances.

[2] Even though the APIs pharmacokinetic behavior is considered in the ERA approach to a certain extent, $F_{EXCRETA}$ only covers the excreted parental compound that enters surface water without considering other emission pathways (such as exhalation).

In this simplified input-/output-analysis, $m_{API(out)}$ is limited to a function of (max.) 5 parameters: DDD and Treatment Period (TP) (depending on the galenic formulation), as well as Excretion Rate (ER), Absorption Rate (AR) and Metabolization Rate (MR) (depending on the API). Other pharmacokinetic processes within the body are not taken into account. Thus, it is assumed that pharmacokinetic data only depend on the API itself (i.e. it has been considered as a substance-specific property in the model), whereas the DDD is determined by factoring in the API and the form of application.

In reality, however, the LADME (liberation-absorption-distribution-metabolism-excretion) process in the body is not only time-dependent but can also be affected by numerous individual aspects such as age, gender, physical condition etc. which are not included in the model. Hence, single values for ER, AR and MR (in %) can be seen as a vast simplification. In reality, a dynamic emission pattern might occur which makes it impossible to compare LCA results with actual measured values. Especially for pharmaceuticals with a very slow release or with controlled release formulations, a significant deviation can be expected. Moreover, the influence of the galenic formulation might be rather insignificant for distribution and elimination processes, but it can affect the absorption/bioavailability (Byers and Sarver 2009; Jung et al. 2021). This aspect should be carefully considered when pharmacokinetic data are obtained.

However, the ERA methodology for medicinal products for human use does not include these effects either. On the contrary, it further simplifies the pharmacokinetic behavior by applying only one value for the excreted quantity of an API ($F_{EXCRETA}$) without particularly considering parameters such as ER, AR or MR.

Having regard to the common practice in ERA, the model appears to be a compromise between the need of a reliable consideration of pharmacokinetic principles on the one hand, and an easy-to-use calculation method within LCI on the other hand. If specific cases (e.g. pro drugs) are assessed, it might be necessary to adjust the calculation rules which is fairly feasible due to its modular structure.

2) EoL modelling of (un-)used pharmaceuticals (waste and waste water treatment)

The choice of a suitable EoL scenario for pharmaceuticals generally depends on the form of application and whether the pharmaceutical has been actually used or not (see second publication, chapter 3.2).

For instance, the application form determines whether the API either ends up in the waste water (if excreted and/or washed off) or in the ambient air (if exhaled) after use. The regular waste management of unused pharmaceuticals, on the contrary, does not necessarily depend on the form of application, whereas the decision to irregularly discard unused pharmaceuticals and the way of disposal can be influenced by physical state (solid/liquid) of the drug (Makki et al. 2019). In the latter

case, the respective inventory flow is then proportionally added to the flows originating from the actual use of pharmaceuticals. It is worth mentioning that the risk for the occurrence of unused pharmaceuticals (and thus, for their improper disposal) can also be affected by numerous other factors, e.g. expiration date and suitability for storage of the product, educational background of the patient, personalized medication or the use of smart drug delivery devices (especially for chronic diseases) etc.

Furthermore, EoL scenarios are highly affected by the geographic scope of the study. The waste management of unused pharmaceuticals, for example, is expected to be a minor emission pathway of APIs to the environment for German conditions and thus, a detailed quantification approach was not presented in this work. However, in some countries, other waste management practices apply which can pose a significant source of API emission (see chapter 4.1.6). If necessary, the current model should therefore be complemented by estimation approaches to take spatial waste management perspectives into account. Especially the EoL scenario 'landfill' can be a relevant potential source of API emissions, mainly through the discharge of contaminated landfill leachate (Yu et al. 2020). A promising starting point to consider these emissions is presented by Cook et al. (2012) who developed a simplified model to calculate the retention of an API depending on its biotransformation and sorption in the landfill body. Furthermore, there are numerous case studies on pharmaceutical emissions from landfill activities which can also provide individually obtained emission factors for pharmaceuticals.

To estimate the behavior of an API in the WWTP, the calculation of distribution factors with SimpleTreat (v.4) is recommended in this work which is again in alignment with the ERA methodology for pharmaceuticals. SimpleTreat has big advantages in this context: It enables not only to calculate removal rates of substances depending on the WWT technology (which is the case for most experimentally designed studies), but to determine distribution rates to air, soil (sludge) and effluent. This is essential for LCA, since potential environmental impacts in all compartments are assessed. Moreover, only few input data are needed which increases the applicability of the tool by decreasing the effort to obtain the necessary data. However, the application of SimpleTreat comes along with some inherent simplifications (e.g. steady state model assuming a linear chemical fate) and thus reveals challenges to accurately predict the behavior of pharmaceuticals in WWTP, particularly to specific pharmaceutical subclasses, such as nanopharmaceuticals (Berkner et al. 2016) and for industrial waste water (Struijs et al. 2016).

The feasibility of SimpleTreat to estimate pharmaceuticals emissions has been comprehensively tested by Lautz et al. (2017): Due to the fact that most pharmaceuticals are ionized or polar (at neutral pH), they have a high affinity to remain in the liquid phase. This has been already included in the revision of SimpleTreat v. 3.1 to the current version by including new Quantitative Structure-Activity

Relationships (QSAR) for sorption. However, concentrations in secondary sludge are still underestimated, mainly due to using the hydraulic retention time instead of the sludge retention time to determine the sludge loading rate in SimpleTreat. (Carballa et al. 2008) also raise concerns on utilizing KOW and KOC values to show the sorption of pharmaceuticals in sewage sludge. Furthermore, SimpleTreat is a steady state model which does not consider time-related variations of important parameters (such as pH-value or content of organic matter). As a result, differences within the WWTP, e.g. for primary settler and secondary sludge, are not represented. Therefore, the authors recommend to utilize average measured values for sludge concentrations instead of calculated values. The prediction of effluent concentrations via SimpleTreat, however, appears to be accurate and is even preferred over measured values. (Lautz et al. 2017)
Other limitations such as neglecting the regeneration of parental compounds through metabolites, potential formation of metabolites or transformation products (e.g. due to photolysis) and the limitation to a standardized three-stage WWTP lead to further deviations from measured values.

It is therefore necessary to critically reflect the results obtained with SimpleTreat with regard to their plausibility. To this end, the following questions could be considered to improve the reliability of the results (based on the findings by Lautz et al. (2017):

- Does the substance under study have a log KOW value that obstructs the applicability of QSAR? If yes, experimental values for the solids-water partition coefficient are preferred.
- Is there any information on the behavior of the parental compound and its metabolites in WWTP (e.g. are there any known transformation products, is there any known reciprocal effect with other substances which are likely to be present in the waste water)? If yes, this information should be considered in the calculation and included in the mass balance. In this case, it might be more expedient to use measured instead of calculated values.
- Are there experimental values for the solids-water partition coefficient, the first order biodegradation constant rate (batch-experiments) and sludge concentration? The experimental setting should be in alignment with the conditions in SimpleTreat. If yes, this data should be preferred to determine the distribution factors.

To a certain extent, modelling simplifications are necessary to reduce the complexity of a real-case scenario. The removal process in a WWTP is indeed very complex, also because waste water often consists of an unknown matrix of countless different (trace) substances. Therefore, a plausibility check (e.g. based on other Measured Environmental Concentrations (MEC) or PEC-values) is always needed to identify potential uncertainties in the model and improve the quality of the LCI. However, SimpleTreat provides fair predictions of removal rates for pharmaceuticals. This is also confirmed by

another comprehensive study by Comber et al. (2019) who combined measured data with calculated values from SimpleTreat for estimating removal rates.

If the distribution factors from SimpleTreat are compared to or complemented by measured values, it should be ensured that only measured values from WWTP effluents are used for comparison since other chemical-physical processes (such as sorption, hydrolysis etc.) can take place in the environmental compartment with a high impact on the results. Moreover, the conditions (e.g. WWTP technology) for the experimental (real) and modelled (SimpleTreat) cases should be equal or at least similar.

It should be noted that SimpleTreat is only recommended to determine the distribution factors (DF) to air, sludge and effluent. Other approaches/tools to model the removal of micropollutants in biological WWTP (e.g. according to Pomiès et al. (2013)), their volatilization or the fate to primary and secondary sludge (Khan and Ongerth 2002) have not been tested here. However, they might provide alternative (or complementary) calculation methods to generate suitable LCI results and therefore need to be further evaluated in the future.

4.2 Practical challenges

In addition to tackling methodological questions of LCA on pharmaceuticals, the criterion of applicability was one important feature within the framework development (see chapter 2.1). Thus, there are no significant deviations between the methodological specifications made in the case study (third publication, chapter 3.3) and those required in the framework. Nevertheless, some practical challenges remain which are discussed in the following chapter.

4.2.1 Sources and availability of inventory data

Even though a systematic analysis of the framework was beyond the scope of the third publication, it revealed some important findings especially with regard to the availability of inventory data which is one of the key challenges in LCA. This has been already mentioned by Jiménez-González and Overcash (2014) who identified the lack of methods to gather inventory data as challenge number one to apply LCA (Jiménez-González and Overcash 2014). Due to limited or non-existent data, several modelling assumptions and simplifications are necessary which may lead to uncertainties of the LCIA results. In that regard, not only data availability but also data quality and deviation can pose practical barriers.

In the case study, qualitative and quantitative data was obtained for production, distribution, use and EoL, whereas primary data was available for the majority of manufacturing and distribution processes (see chapter 3.3). For other production data where no datasets were available in commercial data bases (4 materials for API production, 6 materials for galenic formulation), several approaches to estimate LCI data (e.g. background data for cooling processes) and to justify certain assumptions (e.g. definition of yield losses as production waste) have been identified and applied to the case study (Siegert et al. 2020b). These approaches were later incorporated as additional supportive recommendations in the final framework (Siegert et al. 2019a). However, some of these estimation approaches might be inadequate due to their geographic reference (e.g. Hischier et al. (2005)) or because they rather refer to bulk chemicals instead of fine chemicals and vice versa. Therefore, they should be individually and critically examined with regard to the scope of the study. Nevertheless, they are only examples which can be easily replaced by other tools, calculation methods or data sources.

Due to its novel character, however, specific attention needs to be paid to data which is applied in the use and EoL model. Data availability was also one major reason why the model is based on the existing ERA approach: Since the model is based on calculations which are already part of the approval procedure, it can be assumed that the majority of data needed for the use and EoL model are already obtained by certain bodies (see Table 1) and available e.g. in approval dossiers.

Table 1: Comparison of data required for SimpleTreat and (non-) mandatory base set of data according to the ERA framework.

Substance-specific parameter	Required by SimpleTreat	Required by ERA Guidelines
Chemical class [-]	Y	N
Molecular weight [g · mole^{-1}]	Y	N
Octanol-water particion coefficient (Kow) [-]	Y	Y (according to OECD 107 or 123)
Vapour pressure (Vp) at 298.15 K [Pa]	Y	Y[3] (according to OECD 104)
Solubility (S) at 298.15 K [mg · l^{-1}]	Y	Y (according to OECD 105)
pKa [-]	Y	N (only if log Dow is reported for dissociating compounds)
Henry Law constant (HLC) at 298.15 K [Pa · m³ · mole^{-1}]	Y	N
Organic carbon partition coefficient (Koc) [l · kg^{-1}]	Y	Y (according to OECD 106)
Partition coefficient in raw sewage (Kps) [l · kg^{-1}]	Y	N
Partition coefficient in activated sludge (Kpas) [l · kg^{-1}]	Y	N
Biodegradation rate constant (k biodeg) [h^{-1}]	Y	Y (according to OECD 301, 302, 303b, 310 or 314b)

If specific data are available that fits in the scope of the study, those are therefore preferred over generic data.

[3] Not mandatory

On the downside, the actual access to this data may differ between the different user types of the model (e.g., independent research institutes, API manufacturers etc.) due to confidentiality reasons. Therefore, the data collection (particularly for other less known APIs) remains a challenging task and is identified as one major bottleneck for modelling the use and EoL stage.

Additionally, there is a high variation of data (especially for the distribution in WWTP) which highlights the need of using ranges of values and best/worst case scenarios instead of single absolute values. This, however, leads to tremendous effort for the applicant since data has to be not only collected but the underlying experimental design also needs to be compared with the product system under study (e.g. regarding type of WWTP) to ensure comparability. In the long term, it is therefore inevitable to create a harmonized and globally applicable database which contains both pharmacokinetic and other physico-chemical properties. Furthermore, the definition of best- and worst-case scenarios is not trivial since it depends on numerous (API-specific) factors such as toxicity of parental compound and metabolites which is hard to generally decide within scope definition, especially if there are no information on the environmental risk posed by these substances. The iterative character of LCA is a big advantage in this context. It might be therefore expedient to perform LCIA for different use and EoL scenarios to identify individual best- and worst-case scenarios for each product system instead of providing generic definitions in this framework.

4.2.2 Assessment of (non-)pharma-specific impacts

Another great practical challenge is the assessment of environmental impacts caused by pharmaceutical emissions. The use of LCA to quantify API emissions is currently described as less/not reliable for local emissions, inter alia, because most API emissions could not be properly evaluated with existing impact assessment methods (Pålsson et al. 2019).

This reveals two obstacles: First, completeness and reliability of existing impact categories and assessment methods as well as their suitability for pharmaceuticals. Second, the development/existence of new models to assess pharma-specific impacts.

In the framework, a set of four key indicators and impact assessment models is included which is based on several sources, such as a review of pharma-LCAs, a workshop with experts etc. However, an update of this list revealed the importance of the following impact categories which should be complemented and added to this list: acidification (terrestrial and freshwater), eutrophication, photochemical ozone formation and ozone depletion. Other LCI oriented indicators such as energy use (or cumulative energy demand) and water consumption should also be considered in this amendment. The choice of impact categories and their importance should be verified and further tested in future case studies. Moreover, CFs are needed for these existing impact categories and assessment models to take the potential environmental impacts of pharmaceutical substances into consideration. For the third publication (see chapter 3.3), CFs for ibuprofen (parental compound) could be found, whereas no CFs were available for the metabolites. Consequently, these substances are excluded in LCIA which can pose an underestimation of the use and EoL stage, especially for APIs that are extensively metabolized.

Within this list, also new pharma-specific impact categories are mentioned. One promising approach has been developed by Emara et al. (2021) to take endocrine-related health effects into consideration. To this end, effect factors (EF) and CF are presented for >150 chemicals (Emara et al. 2021). Moreover, Nyberg et al. (2021) recently published their work on how antibiotic resistance could be included in LCA. Nevertheless, the development of other impact assessment models should be accelerated in the future.

5 Conclusion and outlook

Besides their positive effect on human health, pharmaceuticals can also adversely affect the environment during the product´s life cycle. Therefore, it is indispensable to consider not only the occurrence of pharmaceuticals in environmental compartments (which is often limited to pharmaceutical substances in surface water) and the corresponding effects on wildlife and humans, but also potential environmental impacts during API manufacturing, galenic formulation and packaging as well as other potential impacts, e.g. due to an improper disposal of unused pharmaceuticals. This can be achieved by applying the LCA methodology which, however, is not yet harmonized and widely used in the pharmaceutical sector. The goal of this thesis was therefore 'to develop scientifically robust and comprehensive yet applicable rules to guide LCAs of pharmaceutical products and processes'.

To this end, a methodological framework for LCA in the pharmaceutical sector based on the concept of PCR was developed. Existing LCA case studies on pharmaceuticals and other related products, PCRs, as well as sector-specific and generic LCA documents thereby served as a structural and content-related basis. Furthermore, the consideration of life cycle stages beyond manufacturing (in particular: use and EoL stage) has been identified as one major gap in LCA on pharmaceuticals. Hence, a simplified model was presented for the geographic scope 'Germany' to estimate API emissions during and after use of a pharmaceutical as part of the life cycle inventory. Finally, a case study on an ibuprofen analgesic was conducted from cradle to grave to apply the previous results.

This work, thus, significantly contributes to the scientific discourse on the environmental impacts of pharmaceuticals, as a methodological framework is presented which aligns existing approaches and standards, proposes product-related specifications with regard to the LCA method, and allows a more comprehensive environmental assessment from cradle to grave by including a model to estimate API emissions during the use and EoL. Therefore, the LCA methodology for pharmaceutical products is enhanced and, by doing so, the current end-of-pipe focus within ERA is expanded by a more holistic perspective.
On a superordinate, more application-oriented level the results can be used as follows:

- Strengthening the environmental perspective in the authorization process by complementing the usage-centered RA approach and current end-of-pipe focus with a more holistic product-oriented perspective in terms of life cycle data. This also helps to determine the actual relevance of API emissions to the environment from a life cycle perspective. In the case study, for instance, the immense material expenses dwarf the API emissions from use and EoL which appears to be in contradiction to current political and social debates.

- Using the framework to create (more) PCRs by approved program operators and thus, promote EPD development to increase transparency for patients and facilitate ’greener’ purchasing options.
- Increasing sustainability of business decisions by providing streamlined LCA solutions based on a harmonized methodology which support strategic and operational measures (e.g. green procurement, carbon neutrality). The current concern with regard to streamlined tools is that they are often based on incomplete, non-transparent and widely varying methodological specifications. There should be a sector-specific harmonization process regarding the methodology first on which future streamlined tools can be built upon afterwards and not the other way around.

However, some methodological and practical challenges are also identified within this thesis which are discussed in the previous chapter 4. In order to facilitate the application and further development of the framework, the most germane aspects are highlighted in the following paragraphs and recommendations for future research work are given:

Methodological dimension

The **expansion of system boundaries** is already discussed in chapter 4.1.4 but solely limited to R&D activities in the upstream. However, system expansion should also be considered for the downstream, in particular sewage sludge treatment and the subsequent use as fertilizer since this can be another source for pharmaceutical emissions. In this work, emissions occurring from the application of treated sewage sludge to soil are not considered because these flows are assumed to be part of a new product system. However, a separate inventory module should be developed for sludge treatment and the application as fertilizer. This could be then at least disclosed as additional information (e.g. if an EPD is created).

Another focus of future research should be to re-assess the **feasibility of SimpleTreat** and, if necessary, identify alternative calculation tools which allow to determine distribution factors to air, soil and water. The application of SimpleTreat to pharmaceuticals reveals deviations from measured concentrations which is, at least to a certain extent, caused by inherent simplifications of the tool (e.g. neglection of transformation products). It would be also beneficial to allow a higher degree of flexibility to adjust the model, e.g. regarding WWT technology. Thus, a regular update of the tool is indispensable for its future application in this context. In addition, more case studies are needed that systematically evaluate the use and EoL model by applying either SimpleTreat or other tools to identify potential uncertainties and thus, develop further potential for model improvement.

Finally, more **specific rules for pharmaceutical sub-categories** need to be developed to take certain characteristics and differences between sub-categories into account. This would support a better distinction between the sub-categories and hence also contributes to the discussion regarding comparability of pharmaceuticals. To this end, the recommendations according to the first publication can be utilized as an indication where specific rules are needed. A focal point should be the consideration of certain pharma-specific impacts. This, however, requires deeper knowledge of both, the LCA methodology and the particular pharmaceutical sub-category.

Practical dimension

Certainly, one major obstacle for the usability of the framework lies in a limited **data availability** since it affects both, inventory results as well impact assessment results. In this context, not only the absence of data, but also the limited access to this information due to confidentiality reasons is impeding to further develop and apply the LCA methodology on pharmaceuticals. At least, pharmacokinetic information as well as substance-specific data required for the use and EoL model should be available since this information is already obtained within the approval procedure. A harmonized database (e.g. similar to the 'PK-DB' (Grzegorzewski et al. 2021) on pharmacokinetic data, or the database on

pharmaceutical residues in the environment by the German Environment Agency (UBA 2021)) that provides API-specific information on pharmacokinetics as well as risk-related data (see Table 1) would therefore be a huge linchpin. In this context, new monitoring strategies could provide more comprehensive data on the behavior of emerging pharmaceuticals in WWTP. With regard to non-API-specific inventory data, key intermediates and bulk chemicals from pharmaceutical product systems should be identified and datasets need to be developed which are then provided in life cycle data bases.

Moreover, existing impact assessment methods need to be adjusted to take **pharma-specific impacts** into account. Especially the lack of characterization factors for APIs and their main metabolites might lead to an inchoate environmental assessment. Furthermore, missing pharma-specific impact pathways shall be identified and either integrated into existing impact assessment models or new approaches have to be developed.

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Glossary

Absorption Rate

Share of unmetabolized drug which enters the body circulation system after administration (following Alagga and Gupta (2021)).

Active Pharmaceutical Ingredient (API)

Substance in a pharmaceutical product which causes a pharmacological effect.

Allocation

Dividing inputs and outputs of a product system or process between the assessed product system and other product systems (following ISO (2006c)).

By-product

Other products coming from the same product system or unit process (adopted from the definition of a ‘co-product’ by ISO (2006c)).

Defined Daily Dose (DDD)

The average daily amount of a drug needed for its main indication (WHO 2021b).

Elementary Flow

Energy or material flow which leaves or enters the product system to or from the environment without subsequent or previous anthropogenic transformation (following ISO (2006c)).

Environmental Product Declaration (EPD)

Type III eco-label that provides quantitative and qualitative environmental information (following ISO (2006a)).

Excretion Rate

Share of an Active Pharmaceutical Ingredient in its parental or in a metabolized form that is excreted via urine and feces.

Metabolization Rate

Share of an Active Pharmaceutical Ingredient which undergoes a transformation process (i.e. metabolism) within the human body.

Pharmacokinetic Information

Data on properties of a pharmaceutical substance characterizing its absorption, distribution, metabolism, and excretion (following Urso et al. (2002)).

Pharmacovigilance

Monitoring process of a drug´s safety after authorization to detect, assess and prevent adverse effects related to a medicine (following EMA (2021)).

Quantitative Structure-Activity Relationships (QSAR)

Mathematical models to derive information on physicochemical, biological and environmental fate properties of compounds based on their chemical structure (following ECHA (2021)).

Unit Process

Smallest element considered in the life cycle inventory analysis for which input and output data are quantified (ISO 2006b)

List of figures

List of tables

A Appendix

A. 1. Comparison of the Draft PCR and final framework

In the following, methodological aspects are listed where divergent specifications between the first publication ('Draft PCR') and the final framework exist. Additionally, reasons for changing these specifications are provided.

Table A.1.1: Comparison of the Draft PCR and final framework

Methodological aspect	**Draft PCR (Siegert et al. 2018)**	**Final Framework (Siegert et al. 2019)**	**Description**
Definition of the mass-based FU	The 'production of [X] kg API' or 'production of [X] DDD of the pharmaceutical product'	The 'production of [X] kg API' or 'production of [X] DDD of the pharmaceutical product **(packed/unpacked)**'	Packaging ensures the product quality of and can significantly contribute to the LCIA
Dependence of the effect-based FU on goal/intended application:	Yes. If the goal of the study is to perform a hot spot analysis or to identify optimization potentials, a mass based FU can be applied	No (deleted). If a product is assessed, an effect-based FU shall always be applied	To include the therapeutic purpose of the pharmaceutical and strengthen the product-related context, an effect-based FU shall be applied on a product level
Qualitative definition of the use and EoL stage:	The use phase 'shall include the distribution to hospitals or pharmacies […]. The end of life phase shall consider the excretion […] as well as the disposal of expired and unused drugs (including packaging). '	Introduction of a separate module 'distribution'. The use stage starts with the consumption of the pharmaceutical product. It 'ends when the API leaves the human body […] and enters the sewer system and WWTP'. Excretion and the disposal of expired/unused drugs are transition processes which belong to the use stage and convert the product to a waste flow/emission	To be in alignment with the PEF approach, a separate distribution module has been introduced

Pharma-specific impacts	Should be qualitatively reported within the additional information	Shall be qualitatively reported within the additional information	Pharma-specific impacts are essential for a holistic environmental assessment and shall be reported (if additional information is provided)
Additional information	The following additional information shall be considered: side effects, multiple pharmacological effects, and pharma-specific impacts	The following additional information should be considered: side effects, multiple pharmacological effects, pharma-specific impacts, **additional assessment of human- and ecotoxicity, information on carbon storage**	Additional information is crucial if results are intended to be published (e.g. as an EPD). If a study is conducted internally, additional information is optional. The list of additional information is expanded by a further assessment of human- and ecotoxicity since these existing impact assessment models revealed some uncertainties and shall be therefore complemented by different assessment methods. Moreover, information on biogenic carbon storage should be provided (e.g. if herbal pharmaceuticals are assessed)

A. 2. Supplementary material to publication 2

This appendix comprises the supplementary material of publication 2 (Siegert et al. 2020a)[4]:

> Siegert M.-W., Lehmann A., Emara Y., Finkbeiner M. **Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment**. Int J Life Cycle Assess **25**, 1436-1454 (2020). https://doi.org/10.1007/s11367-019-01722-7

[4] Due to a formal error, the supplementary material of publication 2 is not published online.

Table A.2.1: Substance-specific parameter on Ibuprofen for SimpleTreat calculations

Substance-specific parameter	User value	Reference
Chemical class [-]	Acid	(Lautz et al. 2017)
Molecular weight [g · mole^{-1}]	206.285	(PubChem 2019)
Octanol-water particion coefficient (Kow) [-]	3.97 (log Kow)	(PubChem 2019)
Vapour pressure (Vp) at 298.15 K [Pa]	0.0063	(PubChem 2019)
Solubility (S) at 298.15 K [mg · l^{-1}]	21	(PubChem 2019)
pKa [-]	4.91	(PubChem 2019)
Henry coefficient (H) at 298.15 K [Pa · m³ · mole^{-1}]	0.015	(PubChem 2019)
Organic carbon partition coefficient (Koc) [l · kg^{-1}]	224.7 Estimated based on log Kow	Estimated with EPI Suite (KOCWIN) (US EPA 2010, 2012)
Partition coefficient in raw sewage (Kps) [l · kg^{-1}]	67.41	Calculated based on default values provided by Struijs (2013)
Partition coefficient in activated sludge (Kpas) [l · kg^{-1}]	83.139	Calculated based on default values provided by Struijs (2013)

Table A.2.2: Operation-specific parameter on Ibuprofen for SimpleTreat calculations

Operation-specific parameter	User value	Reference
Facility type	Municipal	Scenario set by the authors
Including primary solids removal (default)	Yes	(UBA 2013)

Sewage flow (Q) [$m^3 \cdot d^{-1} \cdot PE^{-1}$]	0.3	Calculated based on data of total waste water in Germany for 2016 (Destatis n.d.), per inhabitant
Mass of sewage solids (SO) [$kg \cdot d^{-1} \cdot PE^{-1}$]	0.09	Default value
Mass of O_2 binding material in sewage (BOD) [$g\ O_2 \cdot d^{-1} \cdot PE^{-1}$]	60	Default value
Sludge loading rate (kslr) [-]	0.1	Default value
pH [-]	7	Default value
Concentration suspended solids effluent [$kg \cdot m^{-3}$]	0.0075	Default value
Type of aeration	Surface aeration	Default value

Table A.2.3: Biodegradation rate for Ibuprofen entered in SimpleTreat

Biodegradation	**User value**	**Reference**
Biodegradation rate (customized)	0.348 (at 293.15 K)	(Urase and Kikuta 2005)

A. 3. Supplementary material to publication 3

This appendix comprises the supplementary material of publication 3 (Siegert et al. 2020b):

> Siegert M.-W., Saling P., Mielke P., Czechmann C., Emara Y., Finkbeiner M. **Cradle-to-grave life cycle assessment of an ibuprofen analgesic**. Sustainable Chem. Pharm. **18**, 100329 (2020). https://doi.org/10.1016/j.scp.2020.100329

Table A.3.1: Pharmacokinetic properties of ibuprofen, 2-hydroxy ibuprofen and carboxy ibuprofen

Substance	Absorption rate [-]	Excretion rate [-]	Metabolizaton rate [-]	Reference
Ibuprofen	0.85	0.1	-	(Ortiz de García et al. 2013)
2-hydroxy ibuprofen	0.85	-	0.37	(Medsafe 2017; Ortiz de García et al. 2013)
Carboxy ibuprofen	0.85	-	0.53	

Table A.3.2: Substance-specific parameter for SimpleTreat calculations

Substance-specific parameter	Ibuprofen	2-hydroxy ibuprofen	Carboxy ibuprofen	Remark
Chemical class [-]	Acid (Lautz et al. 2017)	Acid (HMDB 2020a)	Acid (HMDB 2020b)	-
Molecular weight [g · mole^{-1}]	206.285 (PubChem 2019)	222.28 (HMDB 2020a)	236.26 (HMDB 2020b)	-
Octanol-water particion coefficient (Kow) [-]	3.97 (log Kow) (PubChem 2019)	2.37 (log Kow) (Ferrando-Climent et al. 2012)	2.78 (log Kow) (Ferrando-Climent et al. 2012)	-
Vapour pressure (Vp) at 298.15 K [Pa]	0.00632 (PubChem 2019)	5.62E-5 Estimated	7.2E-5 Estimated	Estimated with EPI Suite (US EPA 2012)
Solubility (S) at 298.15 K [mg · l^{-1}]	21 (PubChem 2019)	300 (HMDB 2020a)	300 (HMDB 2020b)	-
pKa [-]	4.91 (PubChem 2019)	4.63	3.97	-

		(Ferrando-Climent et al. 2012)	(Ferrando-Climent et al. 2012)	
Henry Law constant (HLC) at 298.15 K [Pa · m^3 · $mole^{-1}$]	0.015 (PubChem 2019)	5.62E-7 Estimated	8.6E-8 Estimated	Estimated with EPI Suite (HENRYWIN, bond-method) (US EPA 2012)
Organic carbon partition coefficient (Koc) [l · kg^{-1}]	224.7 Estimated	10.26 Estimated	17.6 Estimated	Estimated with EPI Suite (KOCWIN, Kow method) (US EPA 2010, 2012)
Partition coefficient in raw sewage (Kps) [l · kg^{-1}]	67.41 Calculated	3.078 Calculated	5.28 Calculated	Calculated based on default values provided by Struijs (2013)
Partition coefficient in activated sludge (Kpas) [l · kg^{-1}]	83.139 Calculated	3.796 Calculated	6.512 Calculated	Calculated based on default values provided by Struijs (2013)

Table A.3.3: Operation-specific parameter on ibuprofen for SimpleTreat calculations

Operation-specific parameter	**User value**	**Reference**
Facility type	Municipal	Scenario set by the authors
Including primary solids removal (default)	Yes	(UBA 2013)

Sewage flow (Q) [$m^3 \cdot d^{-1} \cdot PE^{-1}$]	0.3	Calculated based on data of total waste water in Germany for 2016 (Destatis n.d.), per inhabitant
Mass of sewage solids (SO) [$kg \cdot d^{-1} \cdot PE^{-1}$]	0.09	Default value
Mass of O_2 binding material in sewage (BOD) [$g\ O_2 \cdot d^{-1} \cdot PE^{-1}$]	60	Default value
Sludge loading rate (kslr) [-]	0.1	Default value
pH [-]	7	Default value
Concentration suspended solids effluent [$kg \cdot m^{-3}$]	0.0075	Default value
Type of aeration	Surface aeration	Default value

The biodegradation rate for ibuprofen as well as the values for the metabolites are calculated based on the half-life in activated sludge batch experiments presented in (Ferrando-Climent et al. 2012). To this end, the equation for a first order reaction with the initial concentration A_0 and the concentration A at a given reaction time t is utilized.

$$\ln(\frac{[A_0]}{[A]}) = k \cdot t \qquad \text{(Eq. A.3.1)}$$

By applying the half-time $t_{1/2}$ to equation (Eq. A.3.1), the k-value can be determined (see Eq. A.3.2).

$$\frac{\ln(2)}{t_{\frac{1}{2}}} = k \qquad \text{(Eq. A.3.2)}$$

The biodegradation rates are presented in Table A.3.4.

Table A.3.4: Biodegradation rate for ibuprofen, 2-hydroxy ibuprofen and carboxy ibuprofen entered in SimpleTreat

Biodegradation rate (customized)	User value	Reference
Ibuprofen	0.185 (at 292.65 K)	Half-times provided in (Ferrando-Climent et al. 2012)
2-hydroxy ibuprofen	0.185 (at 292.65 K)[5]	Half-times provided in (Ferrando-Climent et al. 2012)
Carboxy ibuprofen	0.347 (at 292.65 K)[5]	Half-times provided in (Ferrando-Climent et al. 2012)

[5] According to Ferrando-Climent et al. (2012), the batch experiments are performed at room temperature between 19 and 20°C. Thus, the arithmetic mean is used in SimpleTreat.

Modelling assumptions – Production stage

- If patents are used and different manufacturing specifications exist (e.g. regarding the amount of catalyst or the reaction temperature), the preferred way to perform the manufacturing is selected.
- Provided default values for a 1000L reactor according to Parvatker et al. (2019) and Piccinno et al. (2016) are utilized and the results are then allocated to the desired amount of (intermediate) product. If a range of values is provided, the conservative (worst) case is chosen
- As a conservative assumption, heat recovery is not considered here, except for the heat recovery from heating itself which is already included in the efficiency of the heating element (Piccinno et al. 2016). However, the temperature of the previous production step is assumed if cooling is not explicitly stated. Thus, heat recovery is taken into account to a certain extent.
- If there is divergent information on the cooling type available (e.g. cooling with air), a simplified thermodynamic calculation based on the heat capacity of the cooling agent is performed.
- We do not explicitly differentiate between fine and bulk chemicals in this case study since there is no common definition of these terms (Wernet et al. 2009).
- If nitrogen is applied as an inert/protective gas but the amount is unknown, it is assumed that it accounts for 10% of the overall reaction mass. This assumption is based on (Piccinno et al. 2016) who presume that only 90% of the reactor volume contains of reaction mass. Hence, the remaining volume is expected to be used to generate an inert atmosphere. After use, nitrogen is assumed to be emitted to air without further treatment
- All other auxiliary materials (such as catalysts) are considered as solid/liquid waste (worst case).
- Hazardous (non-) organic waste is assumed to be incinerated without thermal recovery or landfilled, non-hazardous waste is incinerated in a municipal waste incineration plant (with thermal recovery) or landfilled (only the case for NaCl), metals are recycled. Whether a waste is considered as hazardous or not is individually obtained from material safety data sheets (MSDS). The waste management scenario, however, depends on the regional reference.
- Waste water is emitted to a municipal WWTP without treatment on site
- If possible, the different physical states and related reaction enthalpies (e.g. in case of vaporization, condensation, sublimation etc.) as well as thermodynamic data for the reaction conditions are considered. If this data arenot available, thermodynamic properties such as heat capacities at standard ambient temperature (298.15 K) and pressure (1.013 bar) (SATP) and are used. The standard enthalpy of reaction is only considered if it is explicitly mentioned in the data source and if it is assumed to be relevant for the overall energy balance.

- Differences in reaction pressure (increase or decrease) are only considered for the gaseous reactants. The energy demand for the pressure changes is estimated by applying the ideal gas equation.

$$\Delta p \cdot V = n \cdot R \cdot \Delta T \quad \text{(Eq. A.3.3)}$$

With the volume (V) and number of moles (n) of all gaseous material within the reactor, the gas constant (R) and the known difference in reaction pressure (ΔP), a hypothetical temperature change ΔT is calculated which is than applied to the following equation to calculate the energy demand for heating the reaction mixture:

$$Q_{heat} = m \cdot c \cdot \Delta T \quad \text{(Eq. A.3.4)}$$

Based on this equation, the energy demand Q can be calculated. However, since it is no change in temp. in fact but a change of the reactor pressure, the calculated energy demand is considered as electricity demand and not as heating energy

- If thermodynamic data are available, the influence of a different reactor pressure on the reactants is considered (e.g. change of the boiling point)
- We do not consider potential reaction between auxiliary material or reactants except for the reaction that leads to the desired product.
- The average transportation mix based on (Ecoinvent 2017) is modelled for certain product groups, namely chemicals[6] (basic chemicals and others), waste[6] (haz. and non-haz.), starches, metallic ores, plastic products as well as articles of base metal
- Construction of infrastructure and transport packaging are not included
- Background chemicals are modelled as a global average by employing commercial LCA data bases if their production site is unknown. If global datasets do not exist, EU-specific data are used
- We assume that no API emissions during the production stage occur

Table A.3.5 summarizes the most relevant methods that are used to estimate LCI data of unknown chemicals occurring in the production stage. Furthermore, specifications or modifications of these approaches are described for this case study

[6] For all chemical products, the average of basic chemicals and other chemical products n.e.c. is used. For hazardous waste, the transportation data for non-hazardous waste is applied.

Table A.3.5: Overview of methodological approaches to estimate LCI data of background chemicals

Life cycle stage	Inventory data	Reference	Specification/modification
Production (Inputs)	Masses of substrates, reactants, etc.	-	Upscaled information from patents or other literature Stoichiometric calculations
	Cooling (electricity and other inputs, e.g. make-up water)	(Jiménez-González and Overcash 2000)	Generic cooling tower
	Energy demand for heating	(Parvatker et al. 2019; Piccinno et al. 2016)	Heating energy based on reaction volume of 1,000 L and allocated to 1 kg output
	Energy for stirring, grinding, filtration, drying and transport (pumping)	(Piccinno et al. 2016)	Stirring energy for a reaction volume of 1,000 L Grinding energy: Default value of 16 kWh to^{-1} (worst case) Filtration energy: Default values of 10 kWh to^{-1} (worst case) Transport (pumping) only for gaseous and liquid inputs (except for cooling water)
Production (Outputs)	Production waste	-	Consists of: Yield losses and by-products (following Geisler et al. (2004)) Outputs from cooling tower (i.e. sludge from make-up water pretreatment) (following Jiménez-González and Overcash (2000)) All other auxiliary materials (except for water) (worst case)
	Waste water	-	Consists of: Blowdown water from cooling tower (following Jiménez-González and Overcash (2000)) Waste water occurring from reaction Waste water is emitted to a municipal WWTP (no internal treatment)

Fugitive emissions	Following Jiménez-González and Overcash (2000)	For gases: 0.5% of the input material For liquids: 2% (if boiling point (BP) is between 20 and 60°C); 1% (if BP is between 60 and 120°C) of the input material If BP of a substance is above 120°C, no fugitive loss is assumed Not applied for submodule cooling tower or auxiliary processes (e.g. gas scrubbing) Only applied for inputs Fugitive emissions are not further treated
Product/yield	Following Parvatker et al. (2019)	70% over the entire stoichiometry No differentiation between fine and bulk chemicals; if patent provides detailed information on inputs and outputs, the yield is adjusted

Modelling assumptions – Distribution stage

- Transportation activities by the patient are modeled following the PCR for pharmaceutical products and processes: Purchasing via personal pick up, 5km, by car; single trip solely dedicated to the pharmaceutical product
- Tertiary packaging for transportation purposes is not considered
- For the disposal of unused pharmaceuticals during distribution, a default value (5% of the reference flow) is used. The inventory data related to the upstream processes is adjusted accordingly. This waste stream enters the municipal incineration plant and is assigned to the distribution phase since defective goods are already considered in the production phase
- If some inputs or outputs cannot be clearly assigned to a process, e.g. in the case of multifunctional products/processes or recycling, the generic procedure described in ISO 14044 is applied to avoid these problems (ISO 2006c). If allocation is inevitable, however, it is based on physical relationships (i.e. mass).

Modelling assumptions – Use and EoL stage

- We assume that no expired/unused pharmaceuticals occur during the use stage. This appears to be plausible due to the small packaging size and the short treatment period.
- The use of toilet and other sanitary facilities is not considered because these activities cannot be clearly assigned to the FU
- Since Eudorlin® Extra is sold and used in Germany, sewage sludge from WWTP is expected to be undergo thermal treatment or incineration due to local legislation. All pharmaceutical substances (parental and metabolized) are assumed to be thermally destroyed during these processes (UBA 2019).

Table A.3.6: Additional LCIA results for Eudorlin® Extra (absolute values)

Impact category	LCIA results
CML2001 - Jan. 2016, Abiotic Depletion (ADP elements) [kg Sb eq.]	3.45E-7
CML2001 - Jan. 2016, Abiotic Depletion (ADP fossil) [MJ]	2.23
CML2001 - Jan. 2016, Acidification Potential (AP) [kg SO2 eq.]	0.000515
CML2001 - Jan. 2016, Eutrophication Potential (EP) [kg Phosphate eq.]	0.000139
CML2001 - Jan. 2016, Freshwater Aquatic Ecotoxicity Pot. (FAETP inf.) [kg DCB eq.]	0.0198
CML2001 - Jan. 2016, Global Warming Potential (GWP 100 years) [kg CO2 eq.]	0.14
CML2001 - Jan. 2016, Global Warming Potential (GWP 100 years), excl biogenic carbon [kg CO2 eq.]	0.145
CML2001 - Jan. 2016, Human Toxicity Potential (HTP inf.) [kg DCB eq.]	0.0558
CML2001 - Jan. 2016, Marine Aquatic Ecotoxicity Pot. (MAETP inf.) [kg DCB eq.]	91.2
CML2001 - Jan. 2016, Ozone Layer Depletion Potential (ODP, steady state) [kg R11 eq.]	6.79E-9
CML2001 - Jan. 2016, Photochem. Ozone Creation Potential (POCP) [kg Ethene eq.]	9.97E-5
CML2001 - Jan. 2016, Terrestric Ecotoxicity Potential (TETP inf.) [kg DCB eq.]	0.00266
USEtox 2.1, Ecotoxicity (recommended and interim) [CTUe]	269
USEtox 2.1, Ecotoxicity (recommended only) [CTUe]	0.00228
USEtox 2.1, Human toxicity, cancer (recommended and interim) [CTUh]	5.13E-9
USEtox 2.1, Human toxicity, cancer (recommended only) [CTUh]	1.57E-9
USEtox 2.1, Human toxicity, non-canc. (recommended and interim) [CTUh]	1.08E-7
USEtox 2.1, Human toxicity, non-canc. (recommended only) [CTUh]	5.76E-12

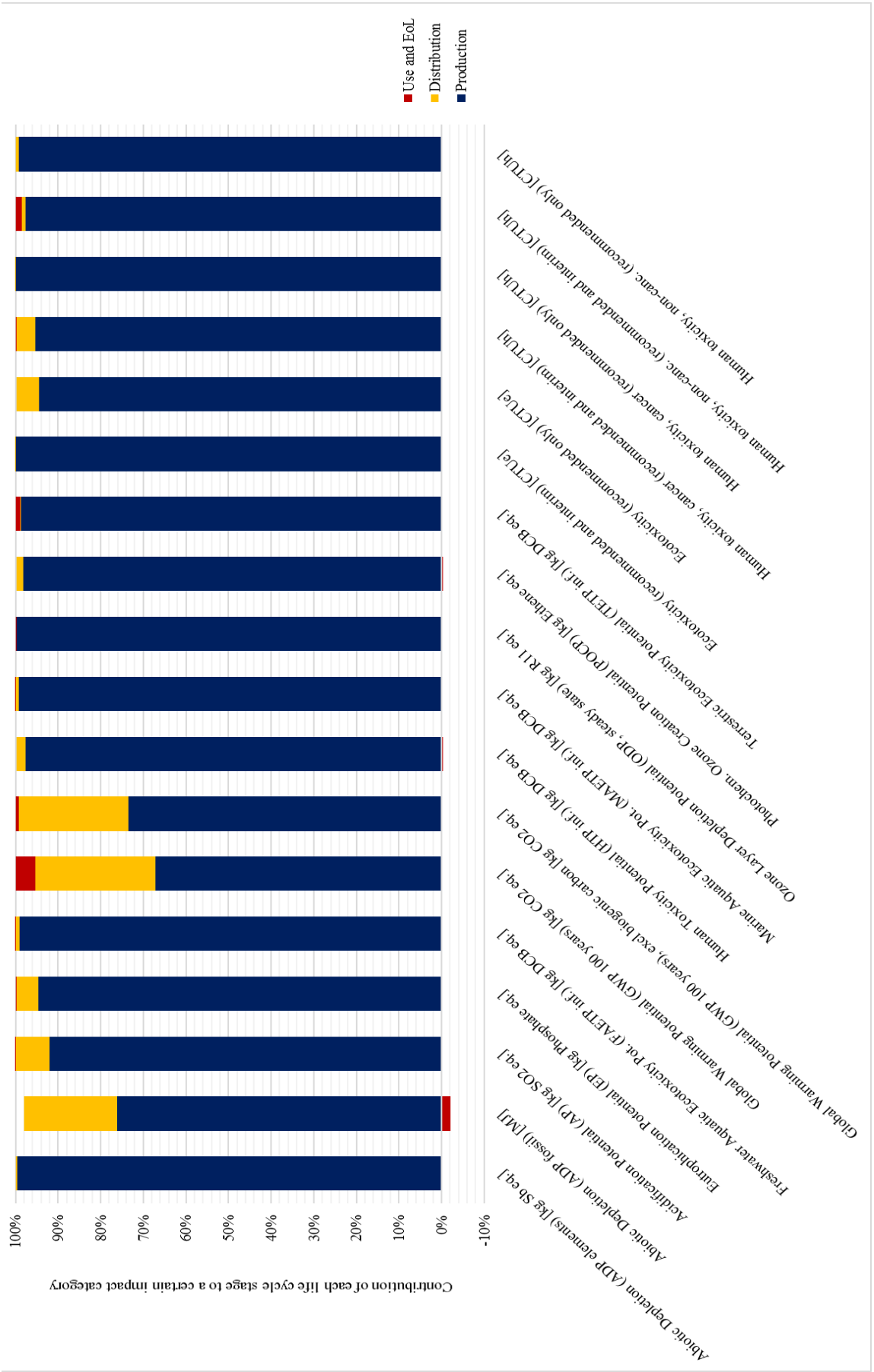
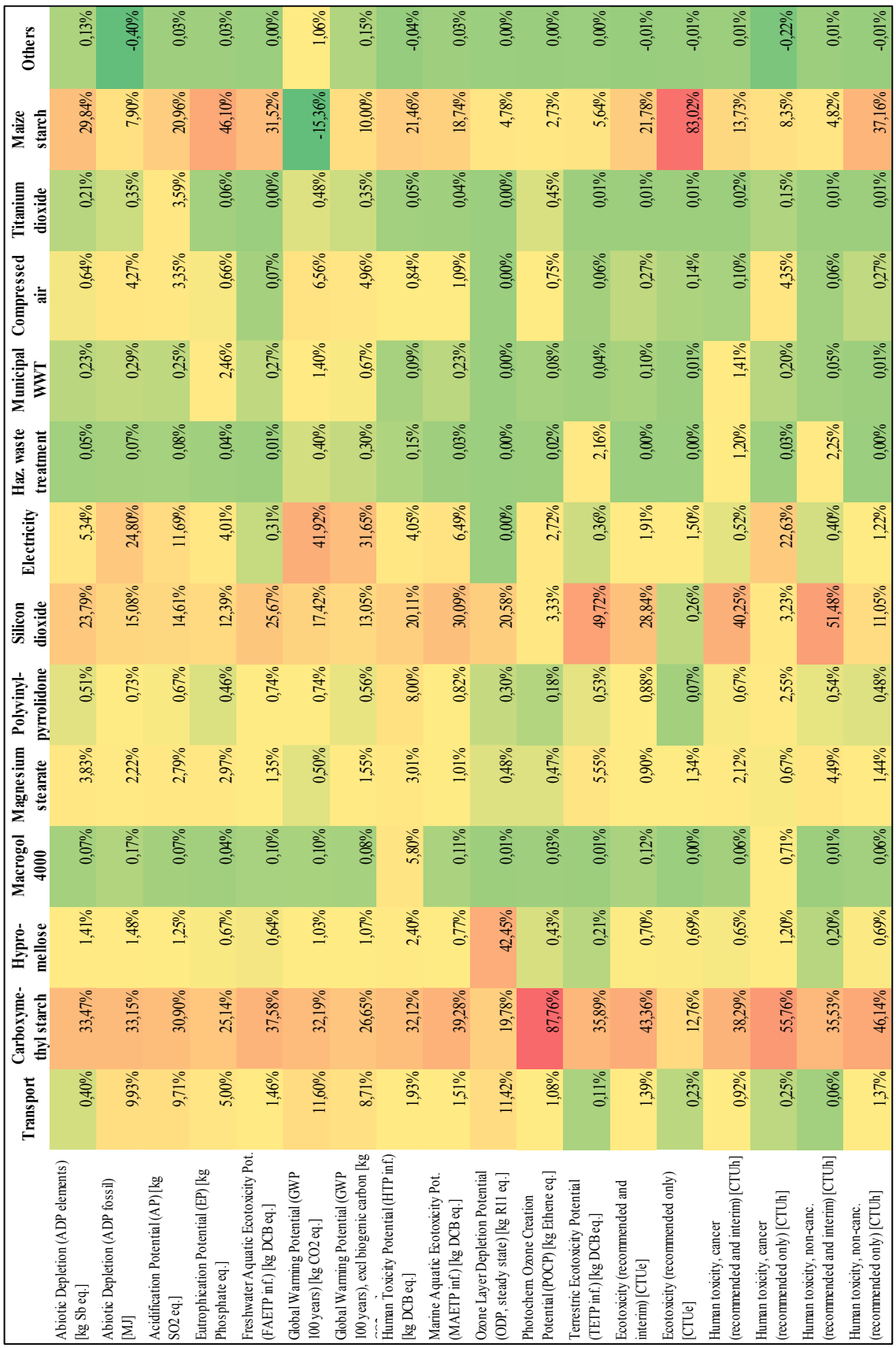


Figure A.3.1: Additional LCIA results for Eudorlin® Extra (relative contribution)



	Transport	Carboxyme-thyl starch	Hypro-mellose	Macrogol 4000	Magnesium stearate	Polyvinyl-pyrrolidone	Silicon dioxide	Electricity	Haz. waste treatment	Municipal WWT	Compressed air	Titanium dioxide	Maize starch	Others
Abiotic Depletion (ADP elements) [kg Sb eq.]	0,40%	33,47%	1,41%	0,07%	3,83%	0,51%	23,79%	5,34%	0,05%	0,23%	0,64%	0,21%	29,84%	0,13%
Abiotic Depletion (ADP fossil) [MJ]	9,93%	33,15%	1,48%	0,17%	2,22%	0,73%	15,08%	24,80%	0,07%	0,29%	4,27%	0,35%	7,90%	-0,40%
Acidification Potential (AP) [kg SO2 eq.]	9,71%	30,90%	1,25%	0,07%	2,79%	0,67%	14,61%	11,69%	0,08%	0,25%	3,35%	3,59%	20,96%	0,03%
Eutrophication Potential (EP) [kg Phosphate eq.]	5,00%	25,14%	0,67%	0,04%	2,97%	0,46%	12,39%	4,01%	0,04%	2,46%	0,66%	0,06%	46,10%	0,03%
Freshwater Aquatic Ecotoxicity Pot. (FAETP inf.) [kg DCB eq.]	1,46%	37,58%	0,64%	0,10%	1,35%	0,74%	25,67%	0,31%	0,01%	0,27%	0,07%	0,00%	31,52%	0,00%
Global Warming Potential (GWP 100 years) [kg CO2 eq.]	11,60%	32,19%	1,03%	0,10%	0,50%	0,74%	17,42%	41,92%	0,40%	1,40%	6,56%	0,48%	-15,36%	1,06%
Global Warming Potential (GWP 100 years), excl biogenic carbon [kg [illegible]	8,71%	26,65%	1,07%	0,08%	1,55%	0,56%	13,05%	31,65%	0,30%	0,67%	4,96%	0,35%	10,00%	0,15%
Human Toxicity Potential (HTP inf.) [kg DCB eq.]	1,93%	32,12%	2,40%	5,80%	3,01%	8,00%	20,11%	4,05%	0,15%	0,09%	0,84%	0,05%	21,46%	-0,04%
Marine Aquatic Ecotoxicity Pot. (MAETP inf) [kg DCB eq.]	1,51%	39,28%	0,77%	0,11%	1,01%	0,82%	30,09%	6,49%	0,03%	0,23%	1,09%	0,04%	18,74%	0,03%
Ozone Layer Depletion Potential (ODP, steady state) [kg R11 eq.]	11,42%	19,78%	42,45%	0,01%	0,48%	0,30%	20,58%	0,00%	0,00%	0,00%	0,00%	0,00%	4,78%	0,00%
Photochem Ozone Creation Potential (POCP) [kg Ethene eq.]	1,08%	87,76%	0,43%	0,03%	0,47%	0,18%	3,33%	2,72%	0,02%	0,08%	0,75%	0,45%	2,73%	0,00%
Terrestric Ecotoxicity Potential (TETP inf.) [kg DCB eq.]	0,11%	35,89%	0,21%	0,01%	5,55%	0,53%	49,72%	0,36%	2,16%	0,04%	0,06%	0,01%	5,64%	0,00%
Ecotoxicity (recommended and interim) [CTUe]	1,39%	43,36%	0,70%	0,12%	0,90%	0,88%	28,84%	1,91%	0,00%	0,10%	0,27%	0,01%	21,78%	-0,01%
Ecotoxicity (recommended only) [CTUe]	0,23%	12,76%	0,69%	0,00%	1,34%	0,07%	0,26%	1,50%	0,00%	0,01%	0,14%	0,01%	83,02%	-0,01%
Human toxicity, cancer (recommended and interim) [CTUh]	0,92%	38,29%	0,65%	0,06%	2,12%	0,67%	40,25%	0,52%	1,20%	1,41%	0,10%	0,02%	13,73%	0,01%
Human toxicity, cancer (recommended only) [CTUh]	0,25%	55,76%	1,20%	0,71%	0,67%	2,55%	3,23%	22,63%	0,03%	0,20%	4,35%	0,15%	8,35%	-0,22%
Human toxicity, non-canc. (recommended and interim) [CTUh]	0,06%	35,53%	0,20%	0,01%	4,49%	0,54%	51,48%	0,40%	2,25%	0,05%	0,06%	0,01%	4,82%	0,01%
Human toxicity, non-canc. (recommended only) [CTUh]	1,37%	46,14%	0,69%	0,06%	1,44%	0,48%	11,05%	1,22%	0,00%	0,01%	0,27%	0,01%	37,16%	-0,01%

Figure A.3.2: Environmental heat map (galenic formulation). The processes are classified based on their relative contribution to the total LCIA result for the galenic formulation. For this purpose, a color scheme from red (large contribution) to green (small contribution) is used.

A. 4. PCR for pharmaceutical products and processes

In the PCR for pharmaceutical products (also referred to as 'final framework'), the results presented in chapter 3 are included and complemented by further (generic) information (e.g. on data quality). The PCR is published under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/):

> Siegert M.-W., Finkbeiner M., Emara Y., Lehmann A. **Product Category Rules (PCR) for pharmaceutical products and processes** (2019). http://dx.doi.org/10.14279/depositonce-9143

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Product Category Rules (PCR) for pharmaceutical products and processes

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[1]

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[1] Taken from Pixabay (2016)

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Table of contents

Figures

Tables

Abbreviations

AMG	Arzneimittelgesetz (medicines law, Germany)
AoP	Areas of Protection
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical classification scheme
BAT	Best Available Techniques
CAS	Chemical Abstracts service
CLP	Classification, labelling and packaging of substances and mixtures
DDD	Defined daily dose
DQR	Data Quality Rating
EC	European commission
EEA	European Economic Area
EoL	End-of-Life
EPD	Environmental Product Declaration
FU	Functional unit
GWP	Global Warming Potential
GPI	General Programme Instructions
HVAC	Heating/Ventilation/Air conditioning
IES	International EPD® System
ILCD	International Reference Life Cycle Data System
IPCC	Intergovernmental Panel on Climate Change
ISIC	International Standard Industrial Classification
ISO	International Organization for Standardization
LCA	Life cycle assessment
OTC	Over the counter
PCR	Product Category Rules
PEF	Product Environmental Footprint
PoE	Point of Emission
R&D	Research and Development
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
Rx	Recipere (lat.), prescription medicine
SU	Sales unit
TP	Treatment period
US EPA	United States Environmental Protection Agency
WBCSD	World Business Council for Sustainable Development
WHO	World Health Organization
WWTP	Wastewater treatment plant

Glossary

Auxiliary material	Material that facilitates the synthesis and feed into the desired product
Comparative assertions	Published statement about the superiority/equivalence of one product compared to others
Core system	Include all gate-to-gate processes that take place within the organization or company, i.e. processes which are in the direct sphere of influence of the developer of the study
Desired product	Product (or intermediate) that is the main reason to run a process and which is needed to fulfil the functional unit
Developer of the study	Organization/ company that manage/runs the gate-to-gate processes and owns the EPD/ LCA study, or external LCA practitioner who creates the EPD/LCA study as a contractor for the organization/company
Healthcare facility	Hospital, nursing home or similar institutions
Methodological requirements	Rules for a product category to conduct an LCA study or create an Environmental Product Declaration (EPD)
Operating material	Material that is necessary to run a process but do not feed into the desired product
Over The Counter-products	Pharmaceutical products which can be purchased without a medical prescription
Preparation	Final pharmaceutical product
Primary data	Data that is collected from the manufacturing plant within the core system, and data from other parts of the life cycle with a direct link to the specific product system under study (e.g. materials by a supplier that is able to provide data), i.e. the process is either runned by the developer of the study or by another company but the developer of the study has access to this specific information
Primary packaging	Packaging that contains the product (direct contact with the preparation)
Producer	Company that actually produces a pharmaceutical product or input material for pharmaceutical processes
Rx-products	Pharmaceutical products which require a medical prescription
Secondary data	Data from commonly available data sources (e.g. databases, proxy/default data)
Secondary packaging	Packaging that contains one or more packed products (no direct contact with the preparation)
Summary of product characteristics	Technical information on a pharmaceutical product
Supporting LCA studies	Studies which are used to develop the PCR
Tertiary packaging	Packaging for the purposes of transport, handling and/or distribution (no direct contact with the preparation)

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1 Introduction

Purpose of this document

This document is intended to define methodological requirements for and provide technical guidance on conducting life cycle assessment (LCA) studies according to ISO 14040/44 or Type III environmental product declarations (EPD) according to ISO 14025 for pharmaceutical products and processes. Thus, it serves as a complementary scientific background document for the application of LCA in the pharmaceutical sector. The intended audience of this document especially includes manufacturer of active pharmaceutical ingeredients (API) and/or galenic formulation and/or pharmaceutical packaging.

Note: This document is not a PCR that is published by an official programme operator. Hence, certain criteria according to ISO 14025, e.g. open stakeholder consultations, are not fulfilled. However, it contains all relevant information that is also included in existing PCR documents which are endorsed by official pogramme operators. Nonetheless, for better readability and reasons of simplicity, we use the term "PCR" to describe this document.

Use of shall, should and may/can

Within the document, the following terminology is used (following the ISO International Standard (ISO 2018) as well as the general programme instructions (GPI) by the International EPD® System (IES 2017)):

- The term "shall" indicates a mandatory rule
- The term "should" indicates a recommendation
- The terms "may" or "can" indicate an option

Structure of the document

This document provides general information (e.g. definition of the product category), background information regarding the PCR development process as well as methodological requirements, i.e. rules for the definition of the goal & scope of the study, the life cycle inventory, the life cycle impact assessment and additional information.

The methodological requirements are described on two different levels. First, generic rules are described that are applicable for all pharmaceutical products **(level I)**. However, depending on the product system assessed, a specification of the methodological requirements for pharmaceutical subgroups may be needed based on the Anatomical Therapeutic Chemical (ATC) classification scheme[2] **(level II)**. For this purpose, specific rules are provided[3] and highlighted in a box. Rules for drug manufacturing processes within this PCR can be seen as an integral part of the generic rules for pharmaceutical products, i.e. the rules on a product level are also valid on a process level. This is illustrated by figure 1:

[2] See chapter 2.3 for further information

[3] This PCR does not define specific rules for each subcategory but indicates the need of further explanation if this is required.

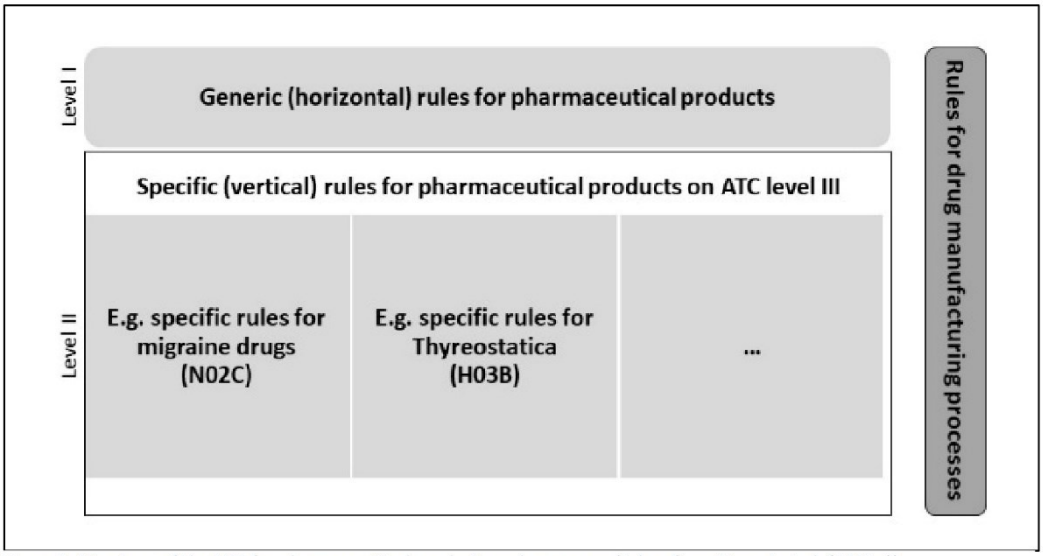

Figure 1: Structure of the PCR for pharmaceutical products and processes (taken from Siegert et al. (2019a))

Furthermore, the following symbols are used:

If additional or different methodological requirements on a process level are needed

If the proposed methodological requirements depend on the goal and intended application of the study, i.e.:

- **Goal:**
  - Comparison of various products/processes
  - Hot spot analysis and optimization of a single product/process
- **Intended application:**
  - Internal application (e.g. product development, decision making support)
  - Publication of results **without** comparative assertions (as an LCA study or EPD)
  - Publication of results **with** comparative assertions (as an LCA study)

2 General Information

2.1 Validity (temporal and geographic)

Temporal validity:

- The PCR developed based on this PCR should be revised after 3 years
- A revision during the period of validity due to general reasons (e.g. editorial changes), fundamental changes within the sector (e.g. regarding the technological representativeness or changes in the underlying legislation) or new LCA based information is generally possible

Geographic validity:

- Production location (manufacturing of API or final preparation): European Union/ European Economic Area (EEA)
- Sales market: Germany

For updating this PCR, the latest versions of documents used for the PCR development shall be utilized. Furthermore, new additional literature and existing PCR shall be identified.

2.2 Conformity with other standards and guidelines

This PCR is consistent[4] with the following standards:

- ISO 14040:2006 (Environmental management - Life cycle assessment - Principles and framework) (ISO 2006b)
- ISO 14044:2006 (Environmental management - Life cycle assessment - Requirements and guidelines) (ISO 2006c)
- ISO 14025:2011 (Environmental labels and declarations - Type III environmental declarations - Principles and procedures) (ISO 2006a)
- ISO/TS 14027:2017 (Environmental labels and declarations - Development of product category rules) (ISO 2017)

In addition, this PCR is intended to supplement and/or is aligned with the following documents:

- Generic standards and guidelines:
  - Product Environmental Footprint Category Rules (PEFCR) Guidance (v. 6.03) (EC 2017b)
  - Guidance for Product Category Rule Development (GPCRD) (GPCRD 2013)
- Sector-specific guidelines:
  - Life Cycle Metrics for Chemical Products (WBCSD 2014)
  - Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices (NHS 2012)
  - Care Pathways: Guidance on Appraising Sustainability (NHS 2015)

An overview of conformity with the aforementioned standards and guidelines is provided in annex, 10.2.

[4] The PCR is considered as consistent with the respective standard if the rules within the PCR are equivalent to, or stricter than the requirements formulated in this standard

2.3 Product category and classification

Following the definition of pharmaceutical products by the European Commission (EC 2001), this PCR is valid for the **product category: pharmaceuticals for human use**, i.e. substances which are used in or administered to human beings to restore, correct or modify physiological functions. Products with the sole purpose to make a medical diagnosis (e.g. X-ray contrast agents), medical devices, food supplements, personal care products, bulk chemicals or veterinary medicine are not covered by this PCR. However, some rules could be also applicable for such similar product groups.

The product classification of pharmaceuticals for human use is conducted according to the Central Product Classification system of the United Nations (UN CPC) (United Nations 2015):

- **Division: 35 - Other chemical products; man-made fibres**
- **Group: 352 - Pharmaceutical products**

The product category shall relate to the function of the product, i.e. products within the product (sub-)category shall have an equivalent function (ISO 2006a; IES 2017).

For this purpose, the **product category: "pharmaceuticals for human use" is further specified by the Anatomical Therapeutic Chemical classification scheme (ATC)[5] based on the therapeutic function of the pharmaceutical product(s)**. Product subcategories are defined by the third level of the ATC classification scheme[6]. To determine the appropriate subcategory of the product that is considered in the study, the developer/commissioner of the study shall comply with the following procedure:

- Identify the API within the product that is assessed and its ATC code (latest version of the ATC classification scheme that is representative for the sales market of the product[7] shall be used)
- Follow the structure up to the third level of the ATC code (e.g. N02C "migraine drugs")
- If a product has several ATC codes, the developer of the study shall decide what the actual therapeutic function of the product is
- The product, its ATC code and the subcategory (based on the third level of the ATC code) shall be cleary stated in the study

Depending on the complexity of the product(s), it might be necessary to further specify the subcategory by considering the fourth level of the ATC system (i.e. the chemical structure of the API) to allow a fair comparison between products. This shall be justified by the developer of the study.

[5] The UN CPC system does not differentiate between pharmaceutical products for human use and veterinary medicine or provides information on the therapeutic function of a pharmaceutical product. However, the ATC classification scheme is globally used by the World Health Organization (WHO) to classify pharmaceutical products based on their API. For this purpose, a unique ATC code is assigned to each API. They are classified on five different levels: The anatomical main group (1st level) describes the organ that is affected, whereas the second and third levels represent therapeutic/pharmacological subgroups. Furthermore, the fourth and fifth level describe the chemical properties of the API (WHO 2017)

[6] Based on expert knowledge, the third level of the ATC scheme enables a proper determination of therapeutic classes. Therefore, APIs with identical third level ATC code can be summarized in specific subcategories due to their equivalent therapeutic functionality.

[7] See chapter 2.1

Only products within the same subcategory (i.e. identical ATC code on the third or fourth level) shall be compared based on their therapeutic purpose

2.4 Product description

The product description shall contain the following information:

- Name of the product (according to medical approval)
- Other trade names if the product is distributed and sold in different countries *(for EPDs only)*
- Name and concentration of the API, as well as other constituents according to summary of product characteristics (see chapter 4.4)
- Dosage form (galenic formulation) (e.g. tablet, capsule, inhalant)
- Defined daily dose (DDD)
- Detailed description of the function of the product(s) within the subcategory:
    - Medical application/indication
    - Route of administration (e.g. orally, rectal)
    - Functionality (pharmacological mode of action) *(for EPDs only)*
    - Application period
- Specification (type and function) of the packaging
    - This shall contain primary and secondary (including packaging size), as well as tertiary packaging (CGF 2011)
    - A statement about the use of recycling material *(for EPDs only)*
- Description of devices to administer the API (e.g. syringes) *(if applicable)*
- Specific storage instructions *(if applicable)*

In addition, the product description should contain the following information:

- Prescription required (y/n)

2.5 Stakeholder participation and communication

A group of experts from industry, science, politics and non-governmental organizations supported this PCR development. However, if this PCR is intended to be published by a programme operator, the stakeholder participation and consultation requirements of the programme operator who publishes the PCR shall be met.
The following institutions, universities, companies and authorities were involved in the PCR development process:

- Deutsche Bundesstiftung Umwelt, DBU (German Federal Environmental Foundation)
- Friedrich-Schiller University Jena
- TH Köln
- TU Berlin
- BASF SE
- Berlin Chemie
- Herbrand PharmaChemicals
- Umweltbundesamt, UBA (Federal Environment Agency)
- Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL (Federal Office of Consumer Protection and Food Safety)

3 PCR Review and background information

3.1 Existing PCR for the same product category

To facilitate harmonization between existing rules, the following PCR was identified and considered within the PCR development process:

- PCR for Vaccines for Human or Veterinary Medicine, whether or not put up as Medicaments
  UNCPC Group: 352 – Pharmaceutical products (IES 2011)
  Programme Operator: International EPD® System; expired on 19 December 2018

Additionally, the underlying PCR Basic module "Other chemical products; man-made fibres) (v.2.5), product category classification UN CPC 35" (IES 2015) and the "General Program Instructions" by the International EPD® system (IES 2017) were considered within the PCR development process.

3.2 Reasoning for PCR development

Before developing this PCR, the option of adopting the existing PCR (see chapter 3.1) according to ISO TS 14027:2017, chapter 6.4.3 (ISO 2017) was examined.

However, the existing PCR will not be adopted due to its limitation to immunological products. Additionally, the PCR is also applicable for veterinary medicine which is not within the scope of this PCR. Moreover, veterinary medicinal products differ from pharmaceuticals for human use (e.g. different therapeutic functions and entry pathways of the API to the environment). Thus, the fundamental principle of products providing the same function within a product category for which category rules are defined is not ensured. Nevertheless, some elements and information within the existing PCR were used to develop the new PCR.

3.3 Supporting LCA studies

According to ISO TS 14027, supporting LCA studies were used to develop the PCR (ISO 2017). For this purpose, case studies of pharmaceutical products (pharmaceutical intermediates, APIs or final drugs, incl. packaging) for human use were considered, even if requirements for supporting LCA studies according to ISO TS 14027, such as conformity with ISO 14040 series or the consideration of all life cycle stages, are not completely met. A comprehensive overview of all supporting LCA studies can be found in annex, 10.1.

4 Goal and scope

4.1 Goal of the study

Generic rule

Some of the methodological requirements in this PCR depend on the goal/intended application of the study. Therefore, goal and intended application shall be clearly described according to chapter 4.2.2 of the ISO 14044 standard (ISO 2006c). In general, the following differentiation is made within this PCR:

- *Goal*:
  - Comparison of *various* products/processes
    Comparisons are only possible, if the products are within the same product subcategory (i.e. share the same ATC-code at the 3rd level), and the functional unit as well as the system boundaries are identical.

    Comparisons on a process level are only possible if the functional unit is identical (i.e. the same product within the system boundaries is produced in different ways)

  - Hot spot analysis and optimization of *a single* product/process (i.e. identification of the relevant processes, elementary flows, impact categories and life cycle stages)
- *Intended application*:
  - **Internal** application (e.g. product development and improvement, decision making support or strategic planning)
  - **External** application (e.g. marketing activities), i.e. publication of results *with or without comparative assertions*

    It shall be considered that comparative assertions are not allowed in an EPD (according to ISO 14025)

4.2 Functional Unit (FU)

Generic rule

The functional unit is defined as the quantified performance of a product system and is used as a reference for all in- and outputs (ISO 2006b). Furthermore, the FU shall be consistent with the goal and scope of the study (ISO 2006c), and shall be identical within a product category (ISO 2006a).

The main purpose of pharmaceutical products is to provide a specific therapeutic function to treat a certain disease (see chapter 2.3). Thus, the functional unit shall be defined as:

- The "treatment of [one or more] [child(ren) or adult(s)] in [geographic region] with [disease/indication] for [period of application]" (**effect-based FU**)
  Example: "The treatment an adult person in Germany with hyperthyroidism for one year."

- The patient, geographic region and duration of treatment shall be defined/specified by the developer of the study
- In addition, the disease shall be specified with regard to the product subcategory (e.g. based on the ATC level III). Other therapeutic functions shall not be considered within the FU definition but can be addressed as "additional information" (see chapter 8).

The reference flow is the required DDD packed[8] and ready for intake, multiplied with the treatment period TP (in days), i.e. the amount of API that is needed to fulfil the therapeutic purpose over a predefined period and, if needed, additional medical devices to administer the drug or additional pharmaceutical products to guarantee the therapeutic effect ("combination preparation")[9]. An extended lifetime due to refurbishment is not applicable for pharmaceuticals but may be relevant for additional devices (e.g. iontophoresis) and should be considered in the study.

If the study is intended to analyze a production process, the functional unit shall be defined as:

- The "production of [X] kg API" or "production of [X] DDD of the pharmaceutical product (packed/unpacked)" (**mass-based FU**[10])
  Example: "The production of one DDD of ibuprofen packed."

- The amount and type of (intermediate) product shall be defined/specified by the developer of the study

In this case, the reference flow is equal to the functional unit.

4.3 Time period

Generic rule

Following the recommendations by ISO TS 14027 (ISO 2017), the product-specific lifetime is determined by the use-by date. This shall be stated by the developer of the study.

If the study is conducted on a process level, a statement on the product-specific lifetime is optional.

4.4 Content Declaration

Generic rule

For pharmaceutical products (final preparation), all materials/substances according to the summary of product characteristics and its average quantitative share (weight % of the final product) shall be listed. If this information is confidential, this shall be clearly stated. In these cases, the weight % of the substances can be anonymized.

Furthermore, potential negative effects on human health or the environment[11] caused by these materials/substances as well as the life cycle stage in which the material/substance is used or released into the environment shall be clearly stated.

If the study analyzes pharmaceutical processes, the developer of the study shall at least describe the API and whether it is suspected to have a negative effect on human health[12] or the environment.

[8] The pharmaceutical packaging is essential to ensure the effectiveness of a medicine. Thus, it shall be included
[9] If this is excluded from the study, this shall be justified by the developer of the study
[10] Also called "Declared Unit" (GPCRD 2013)
[11] According to REACH and/or CLP regulation
[12] Negative effects on human health can occur in patients (e.g. side effects) as well as in indirectly exposed humans

In addition, all materials/substances that are directly used in the API production shall be stated. If these materials/substances are suspected to have a negative effect on human health or the environment, these effects shall be described.
If this information is confidential, this shall be clearly stated. In this case, the names of the substrates can be anonymized.

For internal purposes, a content declaration is not required but may be created.

4.5 Product system

Generic rule

The definition of the product system shall contain the following aspects:

- Description of the life cycle stages
- System boundaries
- Cut off criteria that are applied

The product system shall contain all inputs and outputs (products and elementary flows) crossing the different system boundaries[13]. In addition, this shall be illustrated by a flowchart. In this diagram, the core system shall be marked.

Description of the life cycle stages:

With regard to the geographic, temporal and technical validity, the description of the life cycle stages shall contain:

- The production of precursor/basic chemicals (substrates for API synthesis, operating and auxiliary materials if this information is available) including the extraction of raw material and treatment of production waste/ wastewater,
- The manufacturing of the pharmaceutical product (API production, galenic formulation and packaging) including treatment of production waste
- Transport and distribution (via (hospital-)pharmacies),
- Use (application) and
- End-of-life (EoL) stage of excreted, metabolized or unused/expired[14] products (including waste water treatment and waste treatment of packaging).

If the study investigates pharmaceutical processes only, the transport and distribution, use- and EoL stage should be exluded, if a change of process parameters within the core system does not affect the downstream processes or if these processes are identical. This is further explained under “system boundaries”.

Research & Development (R&D) activities, animal testings, registrations of pharmaceuticals as well as other elements of the treatment pathway (e.g. diagnosis, surgeries etc.) are generally not within the scope of this PCR because these activities are not clearly linked to the use of the pharmaceutical product.

[13] Under consideration of possible cut off criteria
[14] Also called “loss rates” according to PEF Guidance v 6.3, Annex G (EC 2017)

The life cycle stages shall be clearly assigned to the upstream ("cradle to gate"), core ("gate to gate") and/or downstream ("gate to grave") system according to Figure 2 (in alignment with IES (2017)):

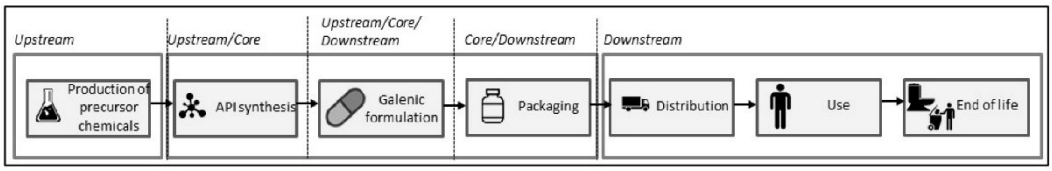

Figure 2: Generic life cycle of a pharmaceutical product

Figure 2 illustrates that API production, galenic formulation and packaging can be elements of the core, upstream and/or downstream system because these production steps are usually performed by different companies. Thus, the developer of the study shall decide how these processes should be assigned and state the name and location of the production site defined as the core system. For this purpose, the following procedure shall be applied:

- The developer of the study produces the API → API synthesis (including transportation of raw and auxiliary material as well as manufacturing waste treatment and power production used for the core processes) shall be defined as the core system. Otherwise it will be defined as upstream process if it is not under direct responsibility of the developer of the study.
- The developer of the study produces the galenic formulation → Galenic formulation (including transportation of API and raw and auxiliary material as well as manufacturing waste treatment and power production used for the core processes) shall be defined as the core system. Otherwise it will be defined as upstream/downstream process if it is not under direct responsibility of the developer of the study.
- The developer of the study produces pharmaceutical packaging → Packaging (including transportation of unpacked drug and raw and auxiliary material as well as manufacturing waste treatment and power production used for the core processes) shall be defined as the core system. Otherwise it will be defined as downstream process if it is not under direct responsibility of the developer of the study.
- The developer of the study produces final preparation → API synthesis, galenic formulation and/or packaging (including transportation of raw and auxiliary material and intermediates as well as manufacturing waste treatment and power production used for the core processes) shall be defined as the core system where it is under the responsibility of the developer of the study

System boundaries:

The system boundaries shall be defined as "**Cradle to Grave"**.

⊙ If the study investigates pharmaceutical processes only, the system boundaries should be **"Cradle to Gate"** including the waste streams generated during the production. However, the factory gate shall be clearly defined according to the previous section, i.e. depending on the definition of the

core system (e.g. “cradle to API” if the API synthesis is defined as the core system). This is also illustrated by the following Figure 3:

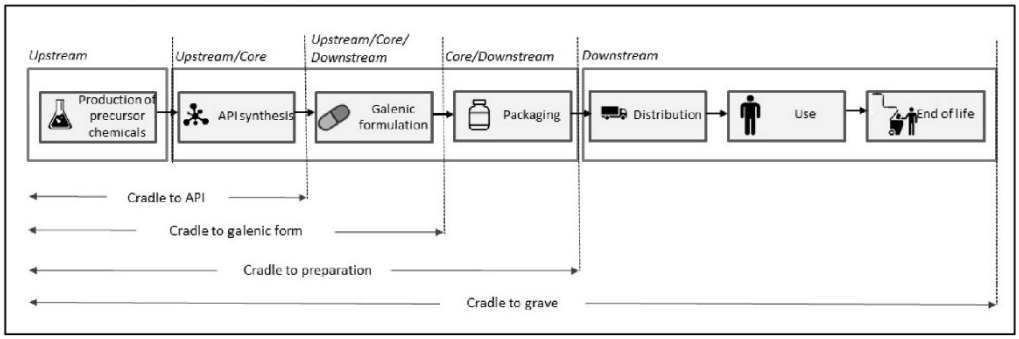

Figure 3: "Gate" definition within the life cycle of a pharmaceutical product (taken from Siegert et al. 2019a))

However, all stage exclusions need to be justified by the developer of the study.

Cut off criteria:

Cut off should be generally avoided (according to GPCRD (2013)). If cut off is necessary due to practical reasons (e.g. data availability), the requirements within ISO 14044, chapter 4.2.3.3.3 shall be considered by the developer of the study (ISO 2006c) and the processes that are excluded shall be described. In addition, the following rules shall be applied for the exclusion of processes, product and/or elementary flows:

- If processes are excluded from the product system this should be done by a **1% cut off** for all impact categories **based on environmental significance**[15], i.e. the contribution of the excludable process to an impact category for any impact category within the impact assessment is less than 1% (in alignment with the PEFCR Guidance 6.3 (EC 2017b)
- The sum of processes which are excluded shall not exceed 5% of the overall environmental impacts
- If a cut off by environmental significance is not feasible, other cut off criteria (e.g. mass) can be applied. This needs to be justified by the developer of the study
- The following processes/substances shall not be excluded:
    - Production processes within the core system
    - Energy inputs used for the production processes within the core system
- The following processes/substances as components of the upstream/downstream system should not be excluded if they significantly contribute to the results:
    - Substances which are classified as toxic to the environment or human health (according to REACH and/or CLP regulation)
    - Processes that generate solid, liquid and gaseous waste and waste water
    - Necessary additional pharmaceutical products (“combination preparation”) or devices which are needed to administer the API (e.g. syringes)

[15] The criterion of environmental significance should be used to avoid that e.g. small amounts of highly toxic substances are excluded from the assessment

If pharmaceutical processes are investigated in the study, downstream processes (e.g. waste and waste water during the consumption stage, additional devices which are needed to administer the API or other pharmaceutical products) should not be considered. Infrastructure, however, should be included on a process level.

Any deviation of these cut off rules (e.g. due to limited data availability or other practical reasons) shall be justified by the developer of the study.

If the study contains comparative assertions intended to be published, other cut off criteria (i.e. mass or energy) shall be additionally applied. In addition, their influence on the overall results shall be examined within the final sensitivity analysis. Comparisons are only allowed if the system boundaries of the product systems are equivalent.

4.6 General data requirements

Generic rule

Data quality requirements:

Generally, two different types of data are required for developing an LCA study/EPD:

1) Data related to the impact assessment (e.g. characterization factors)
2) Inventory data (i.e. in- and outputs crossing the system boundaries)

ISO 14044, chapter 4.2.3.6 lists data quality requirements to meet the goal and scope of the LCA study/EPD. These data quality requirements are applicable for inventory data, and also for impact assessment related data.
The data quality requirements are mainly determined by the temporal and geograpghic validity of the PCR as well as the description of the product system and shall be applied for primary and secondary data:

- Time-related coverage:
  The data should be as up-to-date as possible. The primary data should, at least, represent the last 3 years before developing the LCA study/EPD, secondary data should not be older than 5 years. However, if the product system did not change significantly or only older data is available, this data may be used. This shall be clearly described and justified by the developer of the study
- Geographical coverage:
  The data should be representative for the location where the production step takes place. This should be done according to the following hierarchy:
  - Site-specific data (also referred to as primary data)
  - Average country-specific data (secondary data)
  - Average region-specific data (e.g. Europe) (secondary data)
  - Global average data (secondary data)

  If the location of the production step is unknown (e.g. production of a specific chemical compound in the upstream chain), global average data should be applied. If global data is not available, region- or country-specific datasets can be used.
- Technical coverage:

The data should be representative for the technical state of the art of performing a certain production step on an industrial scale. If this information is unknown, comparable processes or techniques on an industrial or lab scale can be utilized. However, this needs to be justified and analyzed within an uncertainty analysis.

Example: The treatment of solid/liquid waste and waste water shall reflect the actual treatment technology that is used in the product system. If this information is not available, these processes should be modelled according to the current industrial state of the art in the respective region.

Furthermore, the following data quality requirements should be considered (some of the requirements are also applicable for impact assessment data):

- Precision (with regard to measured, calculated and/or estimated data; precision describes the variability of values within a certain data set and should be at +/- 5%)
- Completeness (with regard to all relevant processes within the system boundaries (see also chapter 4.5); this also includes elementary flows and impact categories that shall be considered)
- Representativeness (with regard to geographical coverage, time period and technology coverage)
- Consistency (with regard to all methodological requirements, e.g. the use of aggregated secondary data sets[16], system boundaries, assumptions etc.)
- Reproducibility (for an independent practitioner with regard to the methodological choices and data collection)
- Data sources and collection (with regard to data collection for life cycle inventory and impact assessment; only reliable sources shall be used to derive data (see also chapters 5.1 and 5.2)
- Uncertainty of the information (e.g. with regard to data use, calculation models, assumptions etc.)

◎ If the study contains comparative assertions itended to be published, all data quality requirements according to this chapter shall be taken into account.

Any deviation of these data quality requirements shall be justified by the developer of the study.

Data hierarchy:

Using primary data shall be preferred for modelling the core system/ all processes which are in the direct sphere of influence of the developer of the study, and shall also be preferred for modelling processes within the upstream and downstream system, if available. However, if primary data are not available, verified secondary data (e.g. data from commercial LCA databases, public authorities and industry associations) that are representative for the geographic, temporal and technical scope can be utilized. In some cases, suitable secondary data can be used instead of primary data if the quality of this data is more reliable in terms of the aforementioned quality criteria than the primary data source.

◎ If the study is intended to compare different products or processes, the quality of primary and secondary data sources should be critically examined and compared (e.g. differences regarding measurement procedures). It may be necessary to use identical data sources for the product systems that are assessed to guarantee a fair comparison. Any deviation shall be justified by the developer of the study.

[16] For instance, if an allocation method within the aggregated data set is already applied

Nevertheless, if no appropriate secondary data are available, other secondary data or proxy/default data or calculated values can be utilized. The use of other secondary and proxy/default data and calculated values shall be documented. In addition, the environmental impacts associated with this data should not exceed 10% of the overall env. impacts (in alignment with IES (2017), A5.1). The chapter 5.1 and 5.2 specify all processes for which primary and secondary data are required and how they should be collected.

Handling data gaps:

The treatment of missing data (data gaps) shall be handeled and documented for each unit process by the developer of the study according to ISO 14044, chapter 4.2.3.6.3 (ISO 2006c). In addition, chapter 5.3 of the PCR provides further information on handling missing data.

Evaluation of data quality:

1) ISO 14044 (chapter 4.4.4.2) recommends some techniques to evaluate the life cycle impact assessment related data quality.

2) For the assessment of the data quality of primary and secondary inventory data, a qualitative or semi-quantitative evaluation shall be conducted. In addition to the qualitative or semi-quantitative assessment, an optional quantitative assessment method can be performed. The following data quality assessment methods may be used:

- Semi-quantitative assessment: Pedigree Matrix (Weidema and Wasnaes 1996)
- Quantitative assessment: Data Quality Rating DQR[17] (EC 2017b)

[17] It should be noted that the application of DQR is currently limited to studies within the PEF process. Thus, we suggest to test and discuss this quantitative approach in futute LCA studies based on this PCR.

5 Life cycle inventory

The following subchapters list all life cycle stages and processes, that require primary (subchapter 5.1) or secondary (subchapter 5.2) data. These requirements, however, depend on the definition of the core system (see chapter 4.5). In addition, the developer of the PCR provides a separate data collection sheet in the annex, 10.3.

Example: If the developer of the study is an API producing company, primary data is required for the API production. For precursors chemicals purchased from other companies, primary data are preferred, but secondary data can be used after careful assessment and justification. This also applies to the galenic formulation, if this production step is not under direct operational control of the developer of the study and therefore, part of the downstream system.

5.1 Use of primary data

Generic rule

Primary data shall be separately collected for the following elements within the core system (in alignment with ISO 14044 (ISO 2006c)):

Table 1: Overview of processes that potentially require primary data (depending on the definition of the core system)

Core system	Primary data required	Description
API production	▪ Material input (including substrates, reagents, solvents, catalysts and other auxiliary material) ▪ Operating material ▪ Energy input	Qualitative and quantitative data on the synthesis pathway, the CAS# and quantity used (for each substance), as well as the energy input (for each production step and all services that are somehow related to the production of the desired product, e.g. energy demand of machinery)
	▪ (Co-)Products	Qualitative and quantitative data on the desired product and possible co-products[18]
	▪ Waste (solid/liquid) ▪ Waste water ▪ Direct emissions to air/soil/water	Qualitative and quantitative data on: - Production waste and the treatment pathway - (In-) direct discharge of waste water to municipal waste water treatment plant (WWTP) or industrial WWTP (on site), WWTP technology - Direct emissions, exhaust gas cleaning (on site)
	▪ Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport from (at least) 1st tier supplier to production site - Production waste to treatment plant

[18] see chapter 5.7 for definition of a co-product

Core system	Primary data required	Description
Galenic formulation	▪ Material input (including API, components and other auxiliary material) ▪ Operating material ▪ Energy input	Qualitative and quantitative data on the API, the production of the galenic formulation, the CAS# and quantity used (for each substance), as well as the energy input (for each production step and all services that are somehow related to the production of the desired product, e.g. energy demand of machinery)
	▪ (Co-)Products	Qualitative and quantitative data on the desired product and possible co-products
	▪ Waste (solid/liquid) ▪ Waste water ▪ Direct emissions to air/soil/water	Qualitative and quantitative data on: - Production waste and the treatment pathway - (In-) direct discharge of waste water to municipal WWTP or industrial WWTP (on site), WWTP technology - Direct emissions, exhaust gas cleaning (on site)
	▪ Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport from (at least) 1st tier supplier to production site - Production waste to treatment plant
Packaging	▪ Material input (including preparation, packaging components and other auxiliary material) ▪ Operating material ▪ Energy input	Qualitative and quantitative data on the preparation[19], the production of the packaging, the quantity used (for each substance), as well as the energy input (for each production step and all services that are somehow related to the production of the desired product)
	▪ (By-)Products	Qualitative and quantitative data on the desired product and possible co-products
	▪ Waste (solid/liquid) ▪ Waste water ▪ Direct emissions to air/soil/water	Qualitative and quantitative data on: - Production waste and the treatment pathway - (In-) direct discharge of waste water to municipal WWTP or industrial WWTP (on site), WWTP technology - Direct emissions, exhaust gas cleaning (on site)
	▪ Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport from (at least) 1st tier supplier to production site - Production waste to treatment plant

All data shall be expressed per functional unit or corresponding reference flow. The developer of the study shall clearly state the processes under his/ her operational control for which primary data was collected.

[19] Without packaging

If the developer of the study wants to identify environmental hotspots within the production chain, it may be necessary to collect the following data separately per process: Energy use, direct emissions (to air, water and soil) and generation of (non) hazardous waste. However, if the developer of the study decides to develop a black-box model to calculate the potential environmental impacts of the desired product, overall site-specific inputs and outputs (such as the total energy demand, direct emissions and waste generation of the plant) can be used, which are then allocated to the desired product, e.g. based on the production volume (if other products are manufactured on site)

Potential primary data sources:

The following primary data sources can be used (list is not exhaustive):

- Supplier questionnaire/interviews/audits
- Pharmaceuical manufacturer instructions/approval dossiers
- Measurements/experimental data
- Bill of materials (BOM)
- Invoices/economic data (e.g. companys balance)
- Process simulation tools (e.g. ASPEN Plus®) (if primary data are used as input data)
- Cleaning protocols/batch reports/manuals/operating log/measurements report
- Legal documents (e.g. disposal documents)

5.2 Use of secondary data

Generic rule

If the processes according to chapter 5.1 are not defined as core system, the same data (plus indirect emissions, e.g. due to energy consumption) are required as secondary data. In addition, secondary data shall be separately collected for the following elements within the upstream/downstream system (in alignment with ISO 14044 (ISO 2006c)) if no primary data is available:

Table 2: Overview of processes that potentially require secondary data (depending on the definition of the core system)

Upstream/downstream system	Secondary data required	Description
Production of precursor chemicals	▪ Material input (including substrates, reagents, solvents, catalysts and other auxiliary material) ▪ Operating material ▪ Energy input	Qualitative and quantitative data on the manufacturing process, the CAS# and quantity used (for each substance), as well as the energy input (for each production step and all services that are somehow related to the production of the desired product, e.g. energy demand of machinery)
	▪ (By-)Products	Qualitative and quantitative data on the desired product and possible co-products

Upstream/downstream system	Secondary data required	Description
	▪ Waste (solid/liquid) ▪ Waste water ▪ (In-) direct emissions to air/soil/water	Qualitative and quantitative data on: - Production waste and waste treatment pathway - (In-) direct discharge of waste water to municipal WWTP or industrial WWTP (on site), WWTP technology - (In-) direct emissions, exhaust gas cleaning (on site)
	▪ Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport from resource extraction to production site, and from there to the next costumer - Production waste to treatment plant
Distribution stage	▪ Storage	Qualitative and quantitative data on energy input (e.g. cooling)
	▪ Waste (solid/liquid) ▪ (In-) direct emissions to air/soil/water	Qualitative and quantitative data on: - Waste (unsold/expired products, tertiary packaging) and waste treatment pathway - (In-) direct emissions, exhaust gas cleaning (on site)
	Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport to wholesaler (if applicable), (hospital-) pharmacy[20], and from there to the patient - Production waste to treatment plant
Use stage	▪ Additional devices to administer the API ▪ Energy input (if applicable)	Qualitative and quantitative data on the energy input (for cooling and additional devices)
	▪ Pharmacokinetic data	Qualitative and quantitative data on the pharmacokinetic behavior of the API in the body (e.g. absorption rate) (see also chapter 5.5)
	▪ Waste (solid/liquid) ▪ (In-) direct emissions to air/soil/water	Qualitative and quantitative data on: - Waste (packaging, additional devices, e.g. single-use syringe, regular and irregular disposal of unused/expired drugs) and waste treatment pathway - Direct emissions of API due to exhalation (if applicable) - Other (in-) direct emissions

[20] Considering the scope of the PCR, these are the only ways to distribute pharmaceuticals (see §47 AMG)

Upstream/downstream system	Secondary data required	Description
	▪ Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport from pharmacy/medical practice to patient - Waste to treatment plant
EoL stage	▪ Material input (e.g. precipitants) ▪ Operating material ▪ Energy input	Qualitative and quantitative data on material and energy input (for WWTP and all services that are somehow related to the EoL treatment of the desired product)
	▪ Waste (solid/liquid) ▪ Waste water ▪ (In-) direct emissions to air/soil/water	Qualitative and quantitative data on: - Other waste and waste treatment pathway - (In-) direct discharge of Waste water to municipal WWTP or industrial WWTP (at healthcare facility), WWTP technology - (In-) direct emissions from waste treatment and WWTP (considering exhaust gas cleaning if applicable)
	▪ API-specific data on physical and chemical properties	Qualitative and quantitative data to determine the behavior of the API (and its metabolites) in the WWTP (see also chapter 5.6)
	▪ (Co-)Products	Qualitative and quantitative data on the possible co-products (e.g. sewage sludge as fertilizer, energy due to waste incineration)
	▪ Transports	Qualitative and quantitative data on transport distances, utilization and vehicles for: - Transport from waste treatment plant and WWTP to further processing or final disposal site (e.g. landfill)

All data shall be referred to the functional unit or the corresponding reference flow. The developer of the study shall clearly state the processes for which secondary data was collected. If secondary data is used, double counting (e.g. of emissions) shall be avoided. It is very likely, that methodological choices within aggregated LCA-datasets (e.g. regarding allocation) differ from the rules proposed in this PCR. If possible, these inconsistencies should be avoided. Finally, all sources shall be cited and referenced.

Potential secondary data sources:

The following secondary data can be used (list is not exhaustive):

- LCA Databases (e.g. GaBi, Ecoinvent, European Life Cycle Database, U.S. Life Cycle Inventory Database, Data for Environmental Analsys and Management and other existing LCI datasets (see WBCSD, Appendix 5 A a))
- Generic Databases (e.g. Pharmnet Bund, US EPA, US Departement of Commerce, Economic and Statistics Administration, Department of Transportation, other generic databases [see WBCSD, Appendix 5 A b)])
- Literature (e.g. Römpp encyclopedia, patents [SciFinder, Web of Science, Espacenet], Kirk-Othmer Encyclopedia of Chemical Technology, Ullmann's Encyclopedia of Industrial Chemistry, IHS Chemicals [Chemical Process Economic Program and Chemical Economics Handbook])
- Summary of product characteristics/ leatflet
- BAT documents (e.g. Reference Document on Best Available Techniques for the Waste Treatments Industries durch die EC)
- Reference studies with comparable synthesis routes (e.g. LCAs, EPDs)
- Estimation approaches (e.g. Hischier et al. 2005; Parvatker et al. 2019; Piccinno et al. 2016)
- Process simulation tools (e.g. ASPEN Plus®) or other estimation tools (e.g. Finechem) if secondary data are used as input data

5.3 Handling data gaps

If no primary or secondary data is available, the developer of the study should use approaches to fill these data gaps (e.g. estimations, calculation methods, default values). This is highly relevant for all background data. However, the general data quality requirements and data hierachy (chapter 4.6) shall be met. In addition, the requirements according to ISO 14044, chapter 4.3.3 shall be fulfilled.

The following chapter describes how some of these data gaps can be generally filled and which assumptions are necessary to be made. Most of these approaches are recommended because they are widely used in LCA studies on pharmaceuticals and (fine) chemicals. In addition, default data are provided.

The distribution, use and EoL stages are described separately in chapter 5.4, 5.5 and 5.6

Table 3: Approaches to handle data gaps

Data gap	Assumption[21]	Approach	Default data
Chemical syntheses (e.g. production of basic chemicals or API)	• If production losses are unknown, a process efficiency of 70-95% over the entire stoichiometric equation can be assumed for basic chemicals. • For fine chemicals/pharmaceutical ingredients, a process efficiency of 70% per reaction step can be assumed. If the number of reaction steps is unknown, an overall process efficiency of 3-5% can be assumed	Retrosynthetic breakdown ("chemical tree") (Jiménez-González 2004) on two different levels until all chemical input match with (commercial) datasets: 1. Qualitative level: Literature review (see "potential secondary data sources") 2. Quantitative: Stoichiometric calculation procedure allows determining the unknown masses of basic chemicals if the stoichiometric ratio is known. However, this approach is only feasible for substrates and products but not for other substances like auxiliaries and operating materials. Therefore, it may be necessary to exclude these materials if no further information is available. Other approaches can be found in other existing pharma-LCA studies In addition, subtances resulting from reactions can be either production waste or co-products which should be allocated (e.g. economically if information about their market value are available). This shall be described by the developer of the study (see also chapter 5.7).	N/A

[21] Assumptions are usually product- and/or process-specific to simplify complex facts. Their use as well as value-choices should be generally minimized and clearly stated in the study. In general, the requirements according to ISO 14044, chapter 5.1.1 (ISO 2006c) and ISO 14025, chapter 9.2.1 (ISO 2006a) shall be fulfilled. In addition, assumptions should be consistently applied throughout the study. The effect on the overall results shall be assessed by applying an uncertainty and sensitivity analysis according to ISO 14044 (ISO 2006c). If the study is intended to compare different pharmaceutical products, assumptions regarding the relevant product systems shall be identical.

Data gap	Assumption	Approach	Default data
Energy mix and demand	• Exothermic reactions require the same amount of released energy to cool down the technical equipment • Inherent assumptions within existing simplifying approaches (e.g. by Hischier et al. (2005)) shall be considered if these approaches are used	If the actual purchased energy mix is not available, a commercial dataset representing the country specific power mix should be used The amount of energy needed to run a certain process can be determined by combining process design approaches with basic stoichiometric and thermodynamic calculations (Piccinno et al. 2016). Alternatively, the overall energy demand of a (organic) chemical plant can be estimated based on average data (Gendorf, Germany) (Hischier et al. 2005) or calculated by using the Finechem tool (Wernet et al. 2008; 2012) in case of weak data availability. For cooling energy, the approach by (Jiménez-González and Overcash 2000) for a generic cooling tower can be applied if no further information on the cooling technique is available.	• See Piccinno et al. (2016) • See Hischier et al. (2005) • See Wernet et al. (2008; 2012) • See (Jiménez-González and Overcash 2000)
Other material input (e.g. auxiliary material)	• Inherent assumptions within the simplifying approach by Hischier et al. (2005) shall be considered if this approach is used	Other material input can be obtained from literature/patents or estimated based on average data of a (organic) chemical plant (Gendorf, Germany) (Hischier et al. 2005)	See Hischier et al. (2005)
Transport distances, utilization and vehicles	• Internal transport processes are assumed to be negligible • Inherent assumptions within the simplifying approach by Ecoinvent (2017) shall be considered if this approach is used	If the production steps for precursor chemicals take place in different facilities, the default transport data by Ecoinvent for basic chemicals or other chemical products n.e.c. (Ecoinvent 2017) should be used. Ecoinvent also provides default transport data for non-hazardous waste. If no other data is available, this default data can also be assumed for hazardous waste. For other product groups, the respective data according to Ecoinvent should be utilized. Attention shall be paid if transports are already considered in aggregated datasets	• See Ecoinvent (2017) • Vehicles (transportation with truck): - 32 t lorry (for transports of precursor chemicals) - 22t lorry (for transports of waste)

Data gap	Assumption	Approach	Default data
Infrastructure	On a product level, infrastructure is assumed to be negligible and should be excluded. On a process level, infrastructure (of the manufacturing facility) should be included	The approach of an average chemical plant by Althaus et al. (2007) can be used if infrastructure is considered	See Althaus et al. (2007)
Production waste	• It can be assumed that the disposal pathway complies with the state of the art in the country where the production step takes place • Production waste consists of yield losses and unwanted by-products (Geisler et al. 2004) • According to Hischier et al. (2005), solid waste can be generally omitted if the educts are liquids/gases	The disposal pathway depends on 1) the location of the production site and 2) the type of waste (hazardous/non-hazardous). Reference documents (e.g. Best Available Techniques (BAT) Reference Document for Waste Treatment on a European level (EC 2017a)) or other literature can be used to determine an qualitative proxy for unknown disposal pathways. However, if no qualitative and/or quantitative data on waste generation outside the core system (e.g. during the production of precursor chemicals) is available, the generation of production waste can be estimated based on the approach by Hischier et al. (2005) for an average (organic) chemical plant, or neglected.	For a European production, the following values are proposed as a default value[22]: *Hazardous waste*: 49% to landfill, 6% to incineration (without energy recovery), 7% to incineration (with energy recovery), 38% recycled *Non-hazardous waste*: 48% to landfill, 2% to incineration (without energy recovery), 4% to incineration (with energy recovery), 47% recycled

[22] Default values are provided by calculating the average based of data on waste management in the European Union published by Eurostat (2018)

Data gap	**Assumption**	**Approach**	**Default data**
(In-/direct) Emissions	Inherent assumptions within the simplifying approaches (e.g. by Hischier et al. (2005) and Jiménez-González et al. (2000)) shall be considered if these approaches are used	Emissions to air and water can be estimated based on the approach by Jiménez-González et al. (2000) for fugitive losses. In case of very weak data availability, the approach by Hischier et al. (2005) for an average (organic) chemical plant, or the Finechem tool (Wernet et al. 2008; 2012) can be used	• See Jiménez-González et al. (2000) • See Hischier et al. (2005) • See Wernet et al. (2008; 2012)

Other approaches/ tools to fill inventory data gaps may be found in the underlying LCA studies or other additional sources. If aggregated datasets or simplifying approaches are used, particular attention shall be paid to avoid double counting or inconsistencies between the requirements within the PCR and the methodological choices made by the creator of the dataset (e.g. allocation methods).

◎ If any data is associated with processes that contribute significantly (e.g. more than 30% of one impact category) to the overall results, detailed information on this data with regard to the data quality requirements shall be provided (see also chapter 4.6)

5.4 Distribution stage

According to chapter 4.5, the distribution stage shall generally be considered if a study on product level is conducted.

If the study is intended to analyze a production process or to compare two different manufacturing processes, the distribution stage should be excluded, if a change of process parameters within the core system does not affect the downstream processes or if these processes are identical.

The distribution stage shall contain all transport and storage activities as well as purchasing processes by the consumer (patient). The infrastructure (e.g. manufacturing of the storage facility or roads) should be exluded. Any deviation (e.g. due to limited data availability or other practical reasons) shall be justified by the developer of the study.

The distribution stage is illustrated by the following Figure 4:

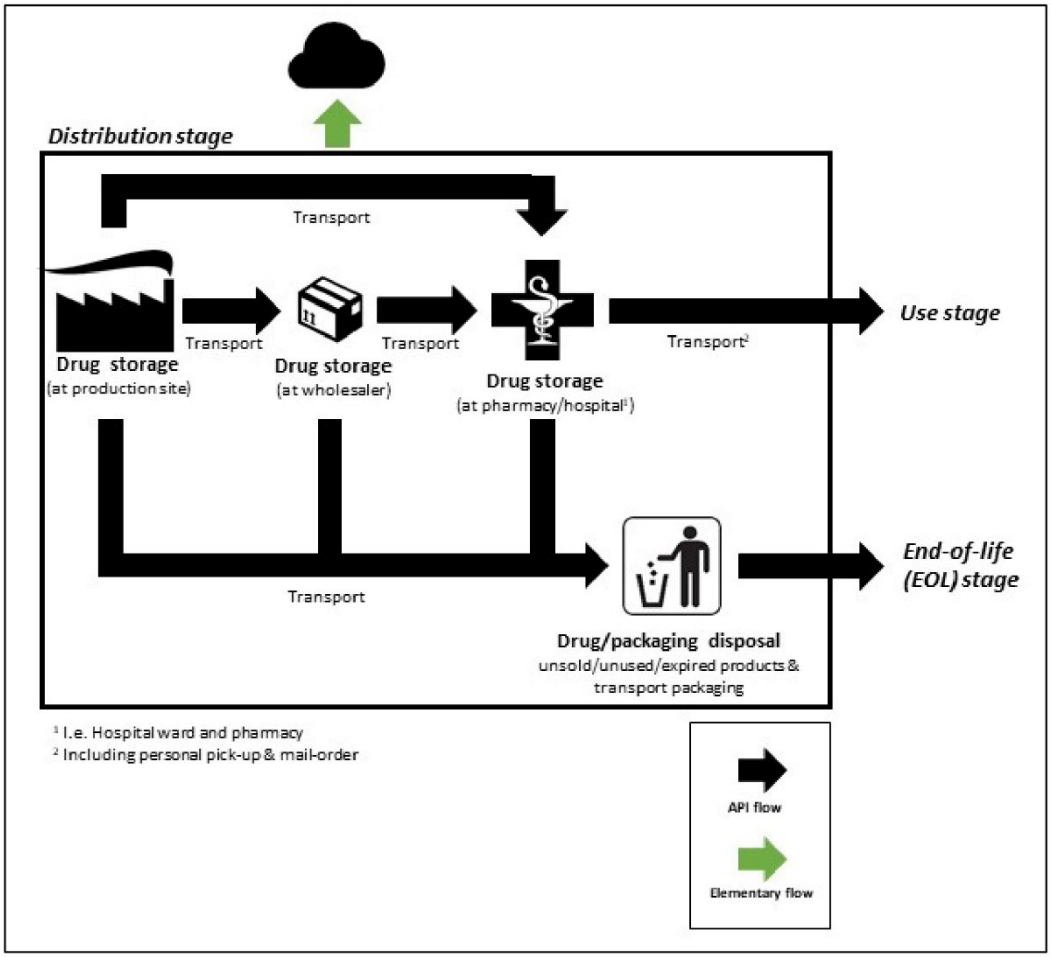

Figure 4: Distribution stage of a pharmaceutical product

Pharmaceutical products can be either distributed indirectly via wholesaler or directly from the producer to (hospital-) pharmacies. Afterwards, the product is sold to the patient via (hospital-)

pharmacies or directly administered in a healthcare facility. This shall be cleary defined by the developer of the study. For this purpose, the following approaches should be used:

- Default approach[23]:
  The distribution of the product to the (hospital-) pharmacy (directly[24] or via wholesaler) and purchasing activities of consumers can be modelled by using default data provided in Table 4.

- Scenario approach[25]:
  Whether the product is distributed directly or indirectly via wholesaler should be defined based on one of the following scenarios:
  - Scenario A: Pharmaceuticals are distributed indirectly via wholesaler, temporarily stored and finally transported to (hospital-) pharmacies
  - Scenario B: Pharmaceuticals are distributed directly from pharmaceutical manufacturer to (hospital-) pharmacies

  Whether the product is purchased in a conventional or hospital pharmacy via personal pick-up or purchased via mail-order should be defined based on one of the following scenarios (only applicable for treatment at home):
  - Scenario C: Pharmaceutical product is purchased by the patient via personal pick-up (from conventional pharmacy or hospital pharmacy)
  - Scenario D: Pharmaceutical product is purchased by the patient via mail-order (from a conventional pharmacy).

If processes in the distribution stage reveals to have a significant impact (e.g. more than 30% of one impact category), the influence of default values/ different scenarios on the overall results should be examined by using a sensitivity analysis.

The distribution stage should include all distribution routes (transport distances, type of vehicle, utilization) as well as energy demand for operating the storage (e.g. cooling the warehouse or cooling during transport). As these rules are part of the PCR, regional differences outside the geographic scope of the PCR are not reflected. The developer of the study, however, should outline if regional aspects could change the results significantly.

The following Table 4 describes the processes within the distribution stage, related assumptions, and provides guidance how the processes can be modelled if no primary or secondary data is available. In addition, default values and scenarios are provided:

[23] One single scenario is defined by the developer of the study based on default data
[24] Direct distribution: Without wholesaler
[25] Different scenarios are defined and calculated by the developer of the study

Table 4:Process description and modelling approaches (distribution stage)

Process	Assumptions	Approach	Default data
Direct distribution from manufacturer to pharmacy or Indirect distribution via wholesaler	• Other distribution pathways[26] are assumed to be negligible (Blasius 2014; BPB 2012). • At this stage, no distinction is made between mail-order/ conventional/ hospital pharmacy, or primary/ secondary wholesaler • Internal transport processes are assumed to be negligible • Inherent assumptions within the approach by Ecoinvent (2017) shall be considered • If cooled storage is required, this is assumed to be also valid for the distribution transport (continuous cold chain) • Specific energy consumption (default) is assumed to be independent of type of packaging • At wholesaler, industrial storage takes place	Pharmaceutical products where a prescription is required (Rx), or "Over the Counter (OTC)" pharmaceuticals are distributed individually. Thus, the distribution pathway of the reference flow should be defined by using the default/ scenario approaches. The mode of transport can be either fixed by the developer of the study or allocated to different possible vehicles according to the default data. The default transport data by Ecoinvent, ISIC No. 2100 (Pharmaceutical products) (Ecoinvent 2017) should be equally used for both, direct and indirect distribution. The storage temperature shall be determined by the developer of the study, e.g. according to the leatflet. The energy demand to provide this storage temperature should be calculated considering the following formula:	• About 15% of the pharmaceuticals are distributed directly whereby the distribution pathway depends on the type of pharmaceutical product. The amount of directly distributed pharmaceuticals consist of 10% Rx-products and 5% OTC-products[27]. • Transport distances: See Ecoinvent (2017) • Vehicle: 22 t lorry • Potential storage temperatures (following (EMA 2007)): - Below 0°C (stored in freezer rooms) - 2-8°C (stored cooled in a refrigerator) - ≤ 25°C (stored in temperature-controlled storage areas) - ≤ 30°C (stored in temperature controlled storage areas) • Specific energy consumption (industrial storage): - 73,5 kWh/m³/year (for frozen products) (adopted from Evans et al. (2014)) - 56,1 kWh/m³/year (for cooled products) (adopted from Evans et al. (2014)) - 0,001 kWh/kg/day (for products stored in temperature controlled storage areas) (adopted from Carlsson-Kanyama (1998))

[26] Due to a low market share and limtation to specific products (e.g. blood derived products, vaccines). In addition, other products according to §44 AMG (e.g. plaster or healing earth), which are distributed via drug stores or supermarkets, do not fulfill the definition of a pharmaceutical products according to chapter 2.3

[27] Based on average data for distribution pathways from 2013-2017 provided by Insight Health (Insight Health 2017). Here, we only differentiate between Rx- and OTC-products

Process	Assumptions	Approach	Default data
	• Storage at conventional and hospital pharmacies can be either industrial or household like	$\text{Energy demand}_{\text{storage}} = \text{Specific energy consumption} * \text{Volume}_{\text{Product}} * \text{Storage time}$ The specific energy consumption and storage time can be determined based on the default data, the volume of the product can be determined according to the leatflet or other sources	• Specific energy consumption (household like, i.e. fridge-freezer combination): - 1,2 kWh/L/year[28] • Average storage time: - 4 weeks (at conventional pharmacy) (PZ 2010) - 3 weeks (at hospital pharmacy) *(expert judgement)* - 2 weeks (at wholesaler) *(expert judgement)*
Purchasing by the patient via mail-order or personal pick-up from conventional pharmacy (if pharmaceuticals administered at home)	• Foreign pharmacies are not considered due to large differences regarding distribution practices (Campos and Galve 2011) • No cooling during pruchasing via mail-order/ personal pick-up can be assumed[29] • Transport on foot and by bicycle are assumed to have no environmental impact • For personal pick-up: Allocation problems due to other purchases	Pharmaceutical products (Rx or OTC) are purchased individually via mail-order or personal pick-up (e.g. via car or public transport). The purchasing pathway of the reference flow should be defined by using the default and scenario approaches. The mode of transport can be either fixed by the developer of the study or allocated to different possible vehicles according to the default data.	• Purchasing behavior depending on the type of pharmaceutical product: - Rx-products: 99% via personal pick-up, 1% via mail-order (BDVA 2018; ABDA 2018) - OTC-products: 87% via personal pick up, 13 % via mail-order (ABDA 2018) • Purchasing distances: - 4-6 km (personal pick-up) (average per federal state according to Neumeier (2013)) - 528-792 km (mail-order)[30] • Vehicles: - Personal pick-up: Bicycle, car (diesel or petrol, Euro 5, engine size 1,4-2), public transport (bus and/or train)

[28] Calculated based on the average (A, A+ and A++) energy consumption of 290 kWh/year (Carbon Footprint 2018) and average fridge volume of 240L

[29] According to DAZ (2017)

[30] Mail-order pharmacies are conventional pharmacies with a specific license. In Germany, 150 pharmacies (6% of all registered pharmacies) professionally participate on mail-order-business (Blasius 2014; BDVA 2018); to calculate the average transport distance to a household, the distance for personal pick-up is multiplied by 132 (factor calculated as the quotient of the number of conventional and mail-order pharmacies according to ABDA (2018))

Process	Assumptions	Approach	Default data
	are not considered because pharmaceuticals are not products for daily needs. Thus, it is assumed that they are purchased separately from other products (e.g. groceries) • For mail-order: Allocation problems occurring from transport of other products (parcels and letters) in the same vehicle should be considered (e.g. inputs/outputs can be allocated based on the weight or volume of the pharmaceutical product)		- Mail-order: Truck (Euro 6, up to 7,5 t) • Mode of transport[31]: - 22% on foot, 11% by bicycle, 56% by car, 11% by public transport
Purchasing by the patient via personal pick-up from hospital pharmacy (if pharmaceuticals administered at home)	• Purchasing on foot or by bicycle is negligible due to the distance to hospital	The purchasing pathway of the reference flow should be defined by using the the default and scenario approaches. The mode of transport can be either fixed by the developer of the study or allocated to different possible vehicles according to the default data.	• Average distance to hospital: 23 km (Albrecht 2011) • Vehicle: Bicycle, car (diesel or petrol, Euro 5, engine size 1,4-2 l), bus or train • Mode of transport: - 22% on foot, 11% by bicycle, 56% by car, 11% by public transport

[31] Based on BMVI (2018); transport mode „car" includes "MIV Fahrer" and "MIVMitfahrer"

Process	Assumptions	Approach	Default data
Disposal of transport packaging and unused[32] products from production sites, wholesaler and (hospital-) pharmacies	• Pharmaceutical products (with primary and secondary packaging) and transport packaging are assumed to be disposed of as non-hazardous commercial waste[33] (see default data) • It can be assumed that the API is completely thermally destroyed after incineration	No reliable data for Germany regarding the disposal of pharmaceuticals exist (Röhreich 5/30/2018). Unused products should be allocated to different disposal pathways based on the default data (see also chapter 5.6) The transport can be modelled based on default transport data by Ecoinvent, ISIC No. 3820 (non-hazardous waste) (Ecoinvent 2017). This approach can be used for the disposal of transport packaging and unused pharmaceutical products (including packaging)	• 5%[34] of the pharmaceuticals produced by the manufacturer, stored by the wholesaler and at the (hospital-)pharmacy remain unsold (amount of unused pharmaceuticals is allocated equally to pharmaceutical production site, wholesaler, (hospital-) pharmacies) • Transport data: See Ecoinvent (2017) - Vehicle: 22t lorry • Disposal pathways: - Transport packaging: 73% recycled, 27% incinerated (with energy recovery)[35] - Unused products: 100% incinerated (with energy recovery) - The incineration takes plance in a municipal solid waste incineration plant

The distribution stage is based on numerous modelling assumptions and thus, characterized by potentially high uncertainties. All assumptions shall be clearly justified and described by the developer of the study. In addition, the data hierarchy according to chapter 4.6 shall be considered.

[32] Expired or unsold; loss rates at consumer are not included in this life cycle stage
[33] This assumption is not valid for cytostatic drugs, vaccine and inhaler. These should be considered as hazardous waste to incineration (without energy recovery) (PZ 2011)
[34] Following the recommendations provided by the European Commission for healthcare products (EC 2017)
[35] Based on UBA (2018b): These default values represent the average disposal pathway of all packaging (not only transport packaging) for the reference year 2016 and can vary depending on the waste fractions that are assessed (e.g. foils, cardboard)

5.5 Use stage

Generic rule

According to chapter 4.5, the use stage shall generally be considered if a study on product level is conducted.

If the study is intended to analyze a production process or to compare two different manufacturing processes, the use stage should be excluded, if a change of process parameters within the core system does not affect the downstream processes or if the use and EoL processes (e.g. excretion pathways of the pharmaceutical product, behavior in the WWTP) are identical.

The use stage shall contain the consumption of the pharmaceutical product by the patient in a healthcare facility or in a household and all related emissions over the treatment period (TP) at the "point of emission (PoE)[36]" (see chapter 4.2). The use stage ends when the API leaves the human body due to excretion or wash off (depending on the route of application) and enters the sewer system and WWTP. In addition, it should include cooling at home/in the healthcare facility during the use as well as the application of devices (e.g. syringe) to administer the API. The manufacturing and use of the toilet or shower (e.g. water to flush), other infrastructure (e.g. manufacturing of the fridge or sanitation), the hands washing process, the consumption of food and drink by the patient as well as patient travels for consulting a doctor should be exluded because these processes can not be clearly assigned to the use of pharmaceuticals. The use stage is illustrated by the following Figure 5:

[36] The PoE can be a healthcare facility (hospital, nursing home and similar institutions) or household. The developer of the study shall clearly define the PoE within the goal & scope phase. It should be considered that the point of administration can differ from the PoE.

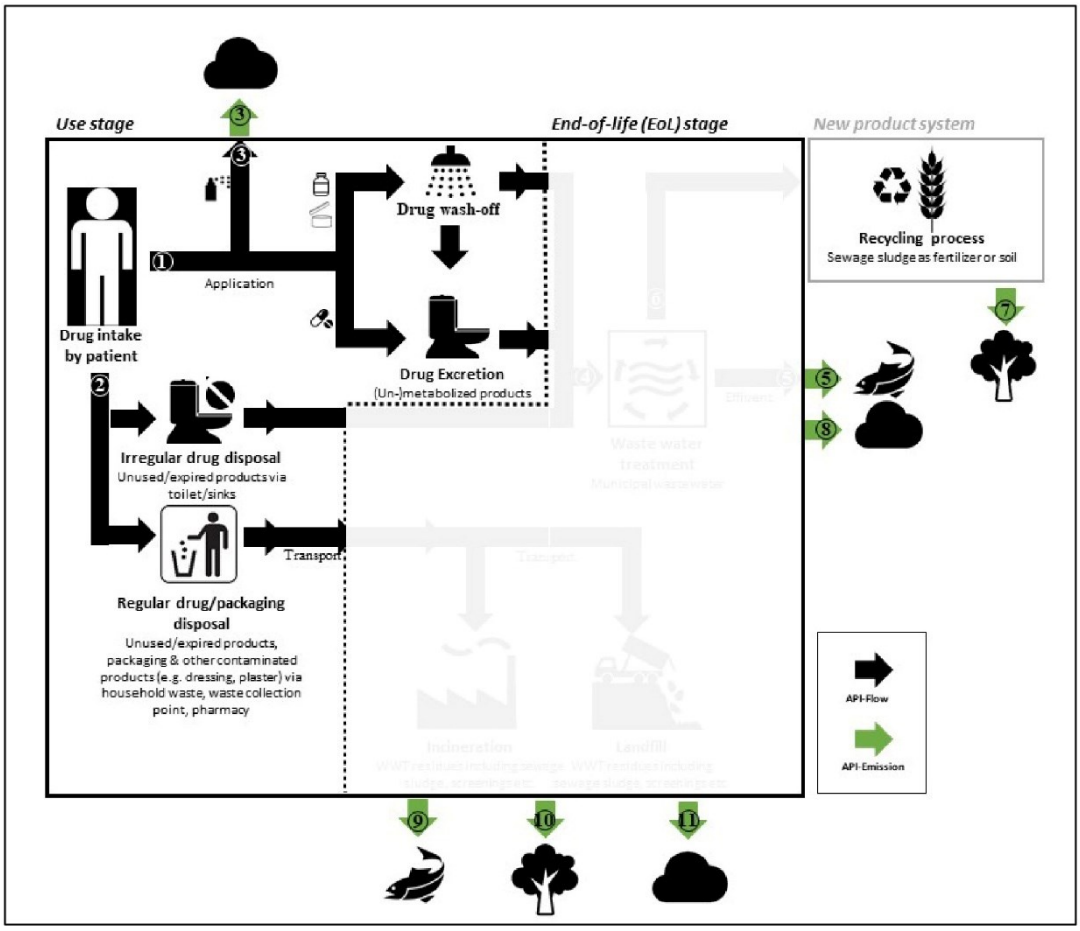

Figure 5: Use stage of a pharmaceutical product (according to Siegert et al. (2019b)). The figure illustrates all API flows and emissions within the use stage (flows #1-3)

To determine all inventory and elementary flows related to the use stage, the developer of the study should consider the approaches and assumptions described in (Siegert et al. 2019b).

In general, the developer of the study shall differentiate between API-flows and emissions[37], and other emissions (e.g. due to the use of additional devices needed to administer the API) that occur during the use stage. Depending on the consumption/emission scenarios (based on the type of disease, dosage form (galenic formulation) and point of emission (PoE)), the API can be emitted to air (elementary flow) due to exhalation, or to WWTP due to excretion or wash off. Complementary to the rules porposed by Siegert et al. (2019b), the following Table 5 describes additional guidance if the use stage is modelled:

[37] In this PCR, we differentiate between API flows within the technosphere (hereinafter called "API flows") and API-specific elementary flows, i.e. API flows between technosphere and ecosphere (hereinafter called "API emissions")

Table 5: Process description and modelling approaches (use stage)

Process	Assumptions	Approach	Default data
Storage of the required dose at home or healthcare facilities during use	• Storage time corresponds to the treatment duration • For cooling at home, household-like conditions according to chapter 5.4 should be assumed (fridge freezer combination), for cooling at healthcare facilities, the assumptions according to chapter 5.4 should be considered	See chapter 5.4	See chapter 5.4 for specific energy consumption
Disposal of packaging (for administered and unused pharmaceuticals)	• In households, primary packaging (no separation) is disposed of via residual waste; secondary packaging (cardboard) is collected and disposed of separately with other paper waste. • In hospitals or other healthcare facilities, primary packaging is disposed of with secondary packaging as non hazardous commercial waste	-	-
Use and disposal of additional devices to administer the API (applicable for households and healthcare facilities)	• Devices to administer the API are either disposed of via residual waste or collected separately as electronic waste	Devices to administer the API can be either single use or reusable items If reusable, the lifetime needs to be defined by the developer of the study The energy consumption (e.g. for electric insulin pumps) should be calculated based on the information obtained from manuals etc.	-

Process	*Assumptions*	Approach	Default data
Regular disposal of unused pharmaceuticals	• In households, unused pharmaceuticals are disposed of via residual waste or local waste collection points[38]; • In hospitals or other healthcare facilities, unused pharmaceuticals are disposed of as non hazardous commercial waste; exceptions, especially cytostatic pharmaceuticals, are classified as hazardous waste and are therefore disposed of seperately	See Siegert et al. (2019b)	See Siegert et al. (2019b) for default data on unused pharmaceuticals and patient´s waste disposal behavior
Irregular disposal of unused pharmaceuticals	• It can be assumed that irregular disposal only occurs in households whereas irregular disposal in healthcare facilities is assumed to be negligible. In case of an irregular disposal, the pharmaceutical product is assumed to be disposed of via sinks and toilets (no differentiation)	See Siegert et al. (2019b)	
Fate in the human body (after drug intake)	• See Siegert et al. (2019b)	See Siegert et al. (2019b)	See Siegert et al. (2019b)

The use stage is based on numerous modelling assumptions and thus, characterized by potentially high uncertainties. All assumptions shall be clearly justified and described by the developer of the study. In addition, the data hierarchy according to chapter 4.6 shall be considered.

◎ If the study is intended to compare different products, the developer of the study shall additionaly state whether a use stage process depends on the product characteristics or not, i.e. is the process qualitatively and/or quantitatively affected by a change of the product characteristics.[39]

[38] According to BMBF (2018). Local waste collection points are assumed to be within walking distance. Thus, no need to model transport activities

[39] See “product independent and dependent processes” according to PEF (EC 2017)

5.6 End-of–life stage

Generic rule

According to chapter 4.5, the EoL stage shall generally be considered if a study on product level is conducted.

If the study is intended to analyze a production process or to compare two different manufacturing processes, the EoL stage should be excluded, if a change of process parameters within the core system does not affect the downstream processes or if processes within the use and EoL (e.g. route of administration, excretion etc.) are identical.

The EoL stage shall contain the treatment of the API in the (municipal) WWTP[40] after excretion, wash off or irregular drug disposal via sinks/toilets, the waste treatment of unused/expired products, packaging of (un-)used products and, if applicable, devices to administer the drug, as well as the treatment of WWTP residues. In particular, API flows and emissions as well as other elementary flows (non-API emissions) occurring in the EoL stage shall be considered. The behavior of the API in sewage sludge during and after processing as well as potential API emissions to soil after land application are part of a new product system and therefore, outside the scope of this PCR. Furthermore, radioactive products (e.g. x-ray contrast media) are also not covered by these rules. All transport processes within this life cycle stage should be included. The manufacturing of infrastructure (e.g. of the WWTP or municipal solid waste incineration plant) shall be exluded because these processes cannot be clearly assigned to the end-of-life of pharmaceuticals. The EoL stage is illustrated by the following Figure 6:

[40] Within this PCR, it is assumed that each household is connected to a public sewer system and municipal WWTP

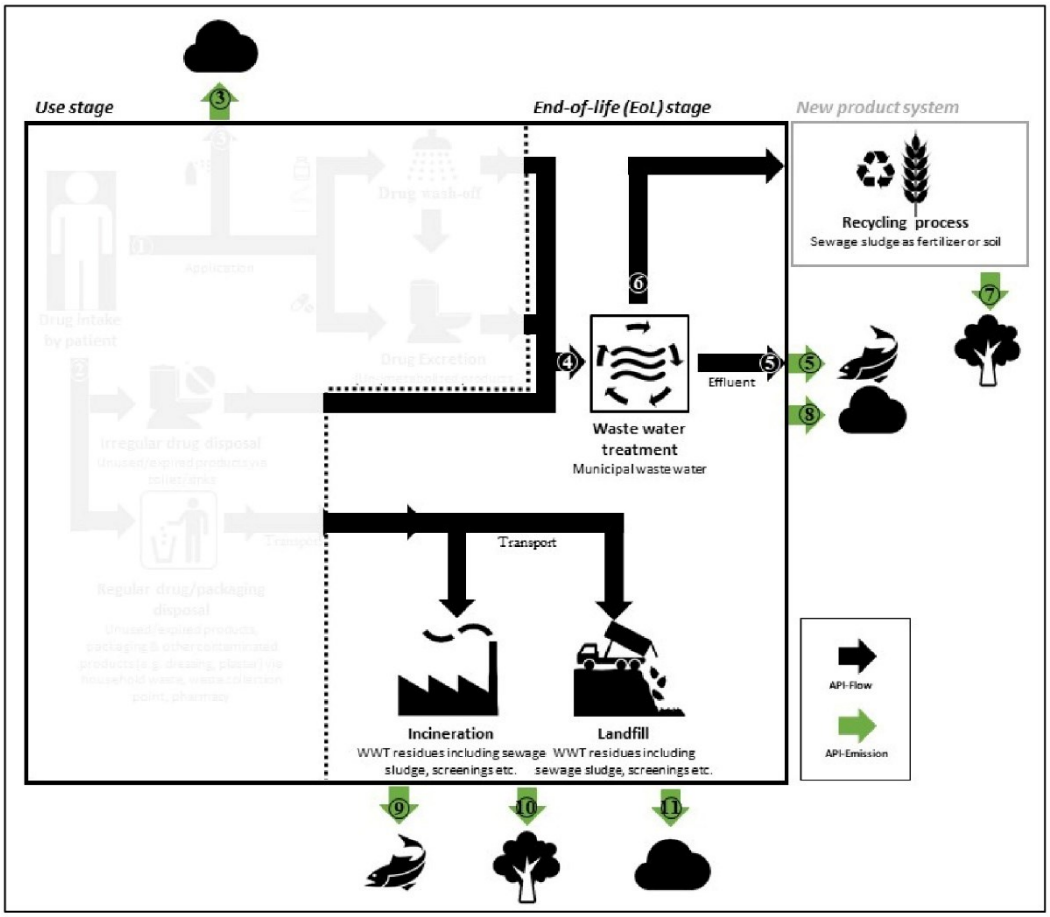

Figure 6: EoL stage of a pharmaceutical product (according to Siegert et al. (2019b)). The figure illustrates all API flows and emissions within the EoL stage (flows #4-11)

The EoL stage depends on the specifications made within the use stage (e.g. regarding disposal behavior of the patient and PoE). To determine all inventory and elementary flows related to the EoL stage, the developer of the study should consider the approaches and assumptions described in Siegert et al. (2019b) for used and unused products. Complementary to these rules, Table 6 describes additional guidance if the EoL stage is modelled:

Table 6: Process description and modelling approaches (EoL stage)

Process	Assumptions	Approach	Default data
Disposal of packaging (of administered and unused products) in households and healthcare facilities	• See chapter 5.5 • API residues that adhere to primary packaging are assumed to be completely thermally destroyed after incineration	The transport can be modelled based on default transport data by Ecoinvent, ISIC No. 3820 (non-hazardous waste) (Ecoinvent 2017). The waste streams should be allocated to the different disposal pathways	• Transport data: See Ecoinvent (2017) • Vehicle: 22t lorry • Disposal pathways: - For healthcare facilities: Primary and secondary packaging: 100% incinerated (with energy recovery) - For households: Primary packaging: 100% incinerated (with energy recovery); Secondary packaging (cardboard): 70% recycled[41], 30% incinerated (with energy recovery) - The incineration process for waste streams from both, households and healthcare facilities takes place in a municipal solid waste incineration plant Further default data according to Siegert et al. (2019b)
Disposal of additional devices to administer the API (from both, households and healthcare facilities)	• Additional devices to administer the API (single use and reusable items) are assumed to be either disposed of via residual waste (without batteries)[42] and incinerated, or collected separately as electronic waste and recycled afterwards	The transport can be modelled based on default transport data by Ecoinvent, ISIC No. 3820 (non-hazardous waste) (Ecoinvent 2017). The waste streams should be allocated to the different disposal pathways	• Transport data: See Ecoinvent (2017) • Vehicle: 22t lorry • Disposal pathways: - Additional devices to administer the API are either reused (depending on their lifetime[43] and the definition of the functional unit), refurbished and recycled and incinerated (for multi-use items), or 100% incinerated (with energy recovery) (for single use items) - Incineration takes place in a municipal solid waste incineration plant

[41] Based on UBA (2018a), 30% are incinerated as residual waste
[42] According to Aponet (2018)
[43] For instance, if the device is used ten times, only 1/10 of the production process of the device is considered as input, 1/10 of the waste treatment process etc.

Process	Assumptions	Approach	Default data
Regular disposal of unused products	• For households, unused pharmaceuticals are either disposed of as residual waste or via waste collection points • For healthcare facilities, unused pharmaceuticals are disposed of as non hazardous commercial waste • Complete thermal destruction of the API after incineration can be assumed • Landfill as final disposal pathway is negligible[44]	See Siegert et al. (2019b) The transport can be modelled based on default transport data by Ecoinvent, ISIC No. 3820 (non-hazardous waste) (Ecoinvent 2017).	• Transport data: See Ecoinvent (2017) - Vehicle: 22t lorry • Disposal pathways: - For households: Unused products: 100% incinerated (with energy recovery) - For healthcare facilities: Unused products: 100% incinerated (with energy recovery) - Incineration takes place in a municipal solid waste incineration plant
Irregular disposal of unused products (via sinks/toilets)	• See chapter 5.5 and Siegert et al. (2019b)	(Siegert et al. 2019b)	See Siegert et al. (2019b)
EoL of used/administered pharmaceuticals	• See Siegert et al. (2019b)	(Siegert et al. 2019b)	See Siegert et al. (2019b)

The EoL stage is based on numerous modelling assumptions and thus, characterized by potentially high uncertainties. All assumptions shall be clearly justified and described by the developer of the study. Furthermore, the developer of the study shall clearly distinguish between waste and co-products. Additionally, allocation problems can occur due to recycling. This is further explained in the following chapter 5.7. In addition, the data hierarchy according to chapter 4.6 shall be considered.

◎ If the study is intended to compare different products, the developer of the study shall additionaly state whether an end-of-life process depends on the product characteristics or not, i.e. is the process qualitatively and/or quantitatively affected by a change of the product characteristics.

[44] Due to the geographic scope of the PCR

5.7 Allocation

Generic rule

Within the allocation step, in- and output flows of a process or product system are assigned to the product system under study and other product systems. Allocation problems occur due to co-products (also referred to as “by-products”), multifunctionality and recycling. For this purpose, the allocation procedures shall be clearly described and the requirements/hierarchy according to ISO 14044, chapter 4.3.4.1 and 4.3.4.2 shall be met. In addition, the following rules shall be considered:

Multifunctional products:

Based on the clear definition of the FU and the assignment of a singular ATC code, confusion about multiple pharmacological effects of the product under study is avoided. However, a statement about possible other medical applications shall be given under additional information.

Multifunctional processes/ co-products:

In an LCA context, co-products are products that result from the same (multifunctional) process. In the modelling process, allocation problems occur, if only aggregated data for a multifunctional process exist (e.g. in case of multi output processes in the production of basic chemicals or if electricity is produced and marketed). To differentiate between co-products and waste, the developer of the study shall consider the “Communication from the Commission to the Council and the European Parliament on the interpretative communication on waste and by-products” (EC 2007) and shall clearly state, which inputs and outputs are considered as waste or co-products (see also figure 5 A 7.3, GPI of the International EPD® system (IES 2017)). If an output cannot be clearly defined as co-product (e.g. if if does not have a downstream application or market value), it should be defined as waste (worst case scenario).

According to ISO 14044, allocation should be avoided by dividing unit processes into several sub-processes and assigning the in- and outputs to these sub-processes. Another way to avoid allocation problems is to expand the product system and thus, include additional functions of the co-product. (ISO 2006c)

If allocation cannot be avoided, the procedure should reflect physical relationship between different products/functions. For this purpose, inputs and outputs should be allocated to the (co-)product based on mass, volume, stoichiometrie or energy (according to WBCSD (2014)). If physical allocation is applied, the developer of the study shall document the physical values that are used.

If physical allocation is not possible or the market prices of the (co-)products differ by more than 20% (average market price over 3 years), inputs and outputs should be allocated based on the economic value, i.e. the average market price over 3 years of the (co-)products (according to WBCSD (2014)). If econcomic allocation is used, the developer of the study shall document the econcomic values that are used.

In addition, a separate sensitivity analysis shall be performed. If the results of the allocation method differ by more than 10% at least for one impact category (according to WBCSD (2014)), another allocation method shall be used. If this is not feasible or the results based on another allocation method

remain unchanged compared to the initial allocation method, the most relevant process parameter and the allocation method should be justified by the developer of the study

Recycling[45]:

If recycling occurs, the generic requirements according to ISO 14044, chapter 4.3.4.3 shall be met. In addition, an open loop recycling should be assumed due to high standards regarding purity, specific characteristics of materials and hygiene requirements in the pharmaceutical sector.

Due to the lack of a sector-specific approach to treat these allocation problems, the Polluters Pay Principle (PPP)[46] should be used. This allocation method reflects the actual legislative situation within the Eurpean Union. i.e. the extended responsibility of waste producer according to the "Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repailing certain directives" (EU 2008). Furthermore, this method is already applied by different programme operators (e.g. International EPD® system). The results shall be analysed within a separate sensitivity analysis.

However, if the recycling appears to contribute significantly to the overall environmental impacts or detailed data about the recycling process is missing, a second allocation method, namely 50/50 allocation split[47] should be applied.

In addition, double counting shall be avoided if secondary material (including recovered energy) is used. In this case, only env. impacts related to the preparation of the secondary material for the use within the studied product system shall be considered.

Allocation problems may occur depending on the pharmaceutical product/product system under study. For this purpose, the proposed allocation methods should be critically examined on a case by case basis.

5.8 Biobased Carbon Storage

Generic rule

The assessment of biogenic carbon should be reported separately. Carbon storage may occur if the product contains biogenic carbon or if atmospheric carbon is taken up by a product (EPD GPI A 9.1.2 (IES 2017)). According to the PEF guidance, no credits associated with temporary carbon storage are given, i.e. emissions within 100 years after their uptake are not considered. Biogenic carbon which is emitted after 100 years, however, shall be considered as permanent carbon storage (PEFCR Guidance v.6.1, chapter 7.9 (EC 2017b)), i.e. credits can be given and shall be modelled according to PEFCR Guidance, B.5.10. According to WBCSD (2014), a carbon credit can appear due to the uptake of CO2-eq. by a plant. The potential emission of this CO2-eq., however, depends on the EoL scenario. The default EoL scenario "incineration" usually leads to a neutral carbon-balance. For an accurate handling, the biogenic carbon along the upstream processes shall be documented and aggregated for the

[45] Includes material recycling, incineration with energy recovery and other recovery (e.g. composting)
[46] Also known as the principle of first responsibility: Producer of the waste carries all environmental impacts until the waste reaches the factory gate of the subsequent user of the waste
[47] Env. impacts and credits due to recycling are equally divided between the product system which produces the waste and the subsequent user of the waste

calculation of the correct biogenic carbon uptake figure. For pharmaceuticals, the effect of biobased carbon storage is presumably low because of the short lifetime and consumption of the products. However, this can be different for other parts of the final preparation, e.g. packaging materials which are made from timber, ending in a longer lasting application after use and recycling. Nevertheless, the calculated figures shall be implemented in the carbon footprint calculation. In addition, carbon storage should be qualitatively reported as "additional information". For further information, ISO/TS 14067:2013 can be utilized.

Depending on the API (e.g. herbal medicine), the developer of the study should explicitly assess the biobased carbon storage according to the aforementioned rules.

6 Impact assessment

6.1 Impact categories, indicators and impact assessment models

Generic rule

An LCIA shall be conducted within studies based on this PCR, and shall be in accordance with the goal and scope phase. The general principles according to ISO 14044, chapter 4.4.1ff. (ISO 2006c) to conduct a life cycle impact assessment (LCIA) shall be met.

The requirements according to ISO 14044, chapter 4.3.2.7 and 4.4.5 (ISO 2006c) (e.g. need of a critical review) shall be met if the study contains comparative assertions.

Based on these requirements, the developer of the study shall, at least, apply the following impact assessment categories and models:

Table 7: Midpoint impact categories and assessment models for pharmaceutical products and processes

Impact category (indicator)[48]	Impact assessment model[49]
Climate change (Global Warming Potential GWP)	▪ IPCC model for Global Warming Potential (GWP) over a 100 year time horizon (IPCC 2013)
Human toxicity (Human Toxicity Potential, cancerogenic / non-cancerogenic)	▪ USEtox model (Rosenbaum et al. 2008; Rosenbaum et al. 2011)
Ecotoxicity (Freshwater aquatic ecotoxicity potential)	▪ USEtox model (Rosenbaum et al. 2008)
Abiotic resource consumption (Abiotic Depletion Potential (ADP) fossil and minerals)	▪ Minerals & metals: ADP model (Guinée 1995; van Oers et al. 2002) (ADP-ultimate reserves) ▪ Energy carriers: ADP model (Guinée 1995; van Oers et al. 2002) (ADP-fossil)
New pharmaspecific impact categories[50]	▪ New characterization models

Considering the geographic scope of the PCR, it can be assumed that no API emissions occur on a process level. Thus, pharma-specific impacts can be excluded.

If other (additional) impact categories or impact assessment models are used, the developer of the study shall reference the related information and sources (ISO 14044, chapter 4.4.2.2.1). If an impact category is not considered, the developer of the study shall exclude its significance and justify the exclusion.

[48] The choice of impact categories is based on a review of pharma-LCAs, a workshop with experts from the pharmaceutical sector, as well as recommendations of the ILCD handbook (EC 2010) and PEF (EC 2017)
[49] The choice of impact assessment models was informed by: (1) recommendations of the ILCD handbook and PEF, (2) their evaluation according to different criteria which were adopted from Lehmann et al. (2016) (e.g. stakeholder acceptance, environmental relevance, applicability) and (3) and a decision tree provided by WBCSD (2014)
[50] The criteria according to ISO 14044, chapter 4.4.2.2.3 should be considered

To supplement the midpoint results according to table 8, the developer of the study can provide **additional** endpoint results (ILCD handbook chapter 10.2 (EC 2010)). These results shall always be presented separately from the midpoint results and for each impact category. The model shall be applied in a consistent way, i.e. using the same model for each impact category. Furthermore, the developer of the study should describe if the results are aggregated based on the Areas of Protection (AoP) like human health, natural environment, natural ressources, or as a single score.

Until today, however, no scientific consensus regarding the use of appropriate endpoint models exist. Thus, no specific endpoint model is recommended within this PCR.


Due to the complexity of cause-effect-chains, endpoint models are generally characterized by high uncertainties and usually based on value choices. Thus, it is not recommended to use endpoint results for communication purposes. If the developer of the study decides to provide endpoint results, they shall always be supplemented by midpoint results. This is also recommended by ILCD handbook, chapter 10.2 (EC 2010).

It may be necessary to apply other/additional impact categories depending on the API and the respective manufacturing process. For this purpose, the developer of the study shall consider the following questions:

1. Is there evidence for other potential environmental impacts due to the product system under study (e.g. land use if herbal APIs are assessed)
2. Which (potential) pharma-specific impacts need to be adressed?

If potential environmental impacts of the pharmaceutical product exist and it is not yet possible to consider these potential impacts within the impact assessment (e.g. nanotoxicity), they shall be qualitatively described as “additional information” (see chapter 8).

6.2 Optional elements

Generic rule

Optional elements as part of the LCIA according to ISO 14044, chapter 4.4.3 are normalization, grouping and weighting, additional LCIA data quality analysis (e.g. uncertainty or sensitivity analysis).

In general, the application of optional elements shall be fully transparent and in accordance with the goal and scope definition. The requirements of the ISO standard shall be met. However, weighting and normalization are subjective and based on value choices. Thus, their application is not recommended. If they are applied in order to support internal decision making in companies, the ISO standard 14044, chapter 4.4.3 shall be followed in a transparent process.


If the results contain comparative assertions, weighting and normalization is not allowed. Furthermore, an uncertainty and sensitivity analysis shall be conducted (see also chapter 7.2).

7 Results and Interpretation

7.1 Results

Generic rule

Taking the goal of the study into account, the developer shall clearly state the audience to whom the results are presented. According to ISO, two types of results exist: a) Life cycle inventory (LCI) and b) Life cycle impact assessment (LCIA) results The general reporting principles according to ISO 14040, chapters 6 and 7 as well as requirements according to ISO 14044, chapters 5.1.1 to 5.1.3 and 5.2 shall be met.


If the study contains comparative assertions, the requirements of ISO 14044, chapter 5.3 and ISO 14040, chapter 6 shall be met. In addition, LCI results only shall not be used for comparative assertions according to ISO 14044.

Furthermore, the following requirements shall be met:

- LCI and LCIA results shall be reported separately and for each process module (life cycle stage or production step[51]) (e.g. reporting env. hot spots for each life cycle stage). An exception is the production of precursor chemicals which can be reported as part of the results of API production.
  All elementary flows related to the five impact categories according to chapter 6.1 shall be listed and their origin examined to identify optimization potentials within the value chain. This is also recommended for internal studies to facilitate the communication of the results.

  
  If a study on a process level is conducted, the results shall be reported separately for each process within the production process/core system that should be optimized to support decision making regarding process optimization measures

- Confidentiality of data can be seen as one of the most critical and limiting aspects if an LCA study is conducted within the pharmaceutical sector. Usually, an LCA study or EPD provides data on an aggregated level. However, if the study is intended to be published but some data shall be kept confidential, the developer of the study shall clearly state which processes/data are treated as confidential.
- Reducing LCA results to a single score by normalization and weighting should be avoided. This result is based on value choices (ISO 14040/44) and is not allowed for comparative assertions (see chapter 6.2)
- The need of a critical review according to ISO 14040, chapter 6 depends on the goal of the study. For studies intended to be used inernally, a critical review can be conducted. It is mandatory if data are published and comparative assertions show the environmental superiority against a competitor's product. In this case, a critical review panel shall be conducted.
- The International System of Units (SI units) shall be applied to express the results.

[51] Depending on the goal of the study and the definition of the core module

- If the results are based on different use- and end-of-life scenarios, the developer of the study shall cleary assign the results to each scenario.

7.2 Interpretation

Generic rule

According to ISO 14044, the interpretation is the last phase of an LCA in which the results are summarized and evaluated to support the decision making process while considering the goal and scope of the study (ISO 2006c). In general, the requirements according to ISO 14040, chapter 5.5 and ISO 14044, chapter 4.5 shall be met.


A comparison of different products and/or processes is only possible, if their context/scope and the assumptions used are equivalent. This shall be assessed before the interpretation phase (ISO 2006c).

The interpretation phase shall contain the elements according to ISO 14044, chapter 4.5.1.1 and 4.5.1.2, i.e.

- Determine significant issues (see ISO 14044, chapter 4.5.2) (ISO 2006c)
- Evaluation of the results (see ISO 14044, chapter 4.5.3) (ISO 2006c)


If the study contains comparative assertions, the specific requirements according to ISO 14044 (e.g. rules on performing the sensitivity analysis[52]) shall be met.

- Conclusions, limitations and recommendations (see ISO 14044, chapter 4.5.4)

Generally, uncertainties and sensitive parameters depend on the product system. For this purpose, the developer of the study shall examine if there is a need for (additional) API specific requirements.

[52] Taken existing pharma-LCAs into account, the following parameters could be sensitive for the overall results of the study: Use of catalysts and solvents, manufacturing of nutrient media, energy demand, sterilization processes, operation modes (batch, continuous) and use- and end-of-life scenarios; sensitivity is expressed as the percentage change of the results by changing predefined parameters. The sensitivity analysis can lead to inclusion/exclusion of certain life cycle stages, processes, in- and output flows

8 Additional information

Generic rule

According to ISO 14025, additional information contains environmentally relevant, product-group-specific information. Additional information can be qualitative and/or quantitative and is neither part of the life cycle inventory nor the impact assessment. However, they shall fulfil the requirements of ISO 14025, chapters 7.2.3 and 7.2.4. The developer of the study should provide the following information:

- Side effects[53]:
  Should be described according to the summary of product characteristics
- Multiple pharmacological function[53]:
  Should be identified according to the ATC classification scheme (including combinations of products) and further described
- Other pharma-specific impacts:
  Should be described if potential environmental impacts can occur during the production, use and/or end-of-life of the pharmaceutical product, and if these impacts are not yet considered within the existing life cycle impact assessment framework (e.g. nanotoxicity)
- Additional assessment of human- and ecotoxicity:
  Should be described by using additional approaches (e.g. ProScale) to complement the impact assessment results
- Information on carbon storage (see chapter 5.8)
  Should be, at least, qualitatively described (whether or not credits are given)

All information shall be referenced.

This additional information is essential for the assessment of the environmental performance of pharmaceutical products and should be considered if the results are intended to be published. If the study is conducted internally, additional information is optional and can be considered.

[53] Due to the consideration of human health as integral part of the environmental impact assessment, these health-related issues are also addressed as additional (environmental) information

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10 Annex

10.1 Documents used for PCR development

Table 8: Overview of documents that served as an input to develop the PCR for pharmaceutical products and processes (following Siegert et al. (2019a))

Type of document	Reference
Generic standards and guidelines	▪ ISO 14025 (ISO 2006a) ▪ ISO 14040/44 (ISO 2006b, 2006c) ▪ ISO TS 14027 (ISO 2017) ▪ Guidance for Product Category Rule Development (GPCRD) (GPCRD 2013) ▪ Product Environmental Footprint Category Rules Guidance (PEFCRG) (EC 2017b)
Sector-specific guideline	▪ GHG Protocol Product Life Cycle Accounting and Reporting Standard (NHS 2012) ▪ Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices (NHS 2015) ▪ Life Cycle Metrics for Chemical Products (WBCSD 2014)
Existing PCR	▪ PCR for Vaccine for human or veterinary medicine, whether or not put up as medicaments (IES 2014)
Existing LCA studies	▪ Pharma-LCAs in accordance with the scope of this PCR (see chapter 3.3): (Amado Alviz and Alvarez 2017; Belboom et al. 2011; Bruggink and Nossin; Brunet et al. 2014; Bunnak et al. 2016; Cespi et al. 2015; Cook et al. 2012; Henderson et al. 2008; Jiménez-González et al. 2013; Jiménez-González 2000; Jiménez-González et al. 2004; Jödicke et al. 1999; De Jonge 2003; Kim et al. 2009; Lee et al. 2016; Llano 2012; Mata et al. 2012; McAlister et al. 2016; Nielsen et al. 2007; Ott et al. 2016; Ott et al. 2014; Pietrzykowski et al. 2013; Poechlauer et al. 2010; Ponder and Overcash 2010; Raju et al. 2016a; Raju et al. 2016b; Ramasamy et al. 2015; Raymond et al. 2010; De Soete et al. 2014a; De Soete et al. 2014b; De Soete et al. 2013; van der Vorst et al. 2013; van der Vorst et al. 2011; van der Vorst et al. 2009; Wernet et al. 2010; Yaseneva et al. 2016; Sherman et al. 2012; Parvatker et al. 2019; Marco et al. 2019)

10.2 Conformity matrix

The PCR is considered as consistent ("green") with the respective standard/guideline if the rules within the PCR are equivalent to or stricter than the standard/guideline, or if the respective requirements are not included in or specified by the standard/guideline. If slight deviations exist, the PCR is considered as partly consistent ("yellow"). However, if the requirements within the PCR do not comply with the standards/guidelines, the requirements are marked as differing/inconsistent ("orange").

Table 9: Conformity matrix PCR

PCR Element	*ISO 14040*	*ISO 14044*	*ISO 14025*	*ISO/TS 14027*	*PEFCR Guidance*	*GPCRD*	*LC Metrics for Chemicals*	*GHG Accounting Sector Guidance*	*Care Pathways: Guidance on Appraising Sust.*
1 Introduction									
2 General Information									
2.1 Validity									
2.2 Conformity w other standards & guidelines									
2.3 Product category & classification									
2.4 Product description									
2.5 Stakeholder participation & communication									

PCR Element	*ISO 14040*	*ISO 14044*	*ISO 14025*	*ISO/TS 14027*	*PEFCR Guidance*	*GPCRD*	*LC Metrics for Chemicals*	*GHG Accounting Sector Guidance*	*Care Pathways: Guidance on Appraising Sust.*
3 PCR review & background information									
3.1 Existing PCR for the same product category									
3.2 Reasoning for PCR development									
3.3 Supporting LCA studies									
4 Goal & scope									
4.1 Goal of the study									
4.2 Functional Unit									
4.3 Time period									
4.4 Content declaration									
4.5 Product system									
4.6 General data requirements									
5 LC Inventory									
5.1 Use of primary data									
5.2 Use of secondary data									

PCR Element	*ISO 14040*	*ISO 14044*	*ISO 14025*	*ISO/TS 14027*	*PEFCR Guidance*	*GPCRD*	*LC Metrics for Chemicals*	*GHG Accounting Sector Guidance*	*Care Pathways: Guidance on Appraising Sust.*
5.3 Handling data gaps									
5.4 Distribution stage									
5.5 Use stage									
5.6 End-of-life stage									
5.7 Allocation									
5.8 Biogenic Carbon Storage									
6 Impact assessment									
6.1 Impact catagories, indicators & impact assessment models									
6.2 Optional elements									
7 Results & interpretation									
7.1 Results									
7.2 Interpretation									
8 Additional Information									

10.3 Data collection sheet

The data collection sheet can be used for LCA case studies in the pharmaceutical sector and is provided as a separate Excel-file. The following information are collected:

- Product system:
  - Consists a manual/instruction for the use of the excel file
  - Required data: Flow chart of the core process and an overall process description
- Product profile:
  - Required data (final preparation): Illustration, trade name and authorization number, packaging size, form of application, concentration of the API, prescription requirements
  - Required data (API): Name, CAS number, ATC code and mode of action
- API production:
  - Required data (generic information): Process scale, operator, location, patent number (if applicable), reference product (output), reference quantity and unit, creation date, reporting period, (expected) annual output of industrial scale production, by-products, flow diagram (API synthesis)
  - Required data (Inputs): CAS#, quantity, unit, information on data collection (e.g. measurements, estimations, calculations etc.) (for substrates, reagents, solvents, catalysts, other additives and operating materials). In addition, information on infrastructure (if applicable) and energy inputs (including way of energy production) are required
  - Required data (Outputs): Quantity, unit and data collection (for products, liquid/solid waste, wastewater, emissions to air, to water and to soil). In addition, information on disposal routes for liquid/solid waste streams, WWTP and flue gas treatment is required
  - Required data (Transport): Quantity, unit, distances, mode of transport and capacity
- Galenic formulation: See “API production”
- Packaging:
  - Required data (generic information): Process operator, quantity of drug per packaging unit, reference product (output), reference quantity and unit, creation date, reporting period, (expected) annual output of industrial scale production, by-products, flow diagram (packaging)
  - Required data (Inputs): quantity, unit and information on data collection (for material input, operating materials, infrastructure). In addition, information on energy inputs (including way of energy production) are required
  - Required data (Outputs): See “API production”
  - Required data (Transports): See “API production”
- Storage and distribution:

- Required data (generic information): Total sales volume per year and storage temperature
- Required data (Transport): Sales market, quantity, unit, distance, mode of transportation, capacity

- Use and EoL:
  - Required data (generic information): Area of application, DDD, duration of use, instructions for storage and disoisal
  - Required data (pharmacokinetic properties): Excretion rate, metabolization rate, name(s) of metabolite(s), absorption rate
  - Required data (chemical-physical properties): Chemical class (i.e. acid, base, neutral), molar mass, Kow-value, vapor pressure, solubility, pKa value, Henry coefficient, Koc-value, Kps-value, Kpas, value and biodegradation rate