Product Category Rules (PCR) for pharmaceutical products and processes

Date: 13 December 2019

This work is licensed under a Creative Commons Attribution 4.0 International License

DOI: http://dx.doi.org/10.14279/depositonce-9143

\(^{1}\) Taken from Pixabay (2016)
**Authors:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Contact:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegert, Marc-William</td>
<td>Technische Universität Berlin - Chair of Sustainable Engineering</td>
</tr>
<tr>
<td>Finkbeiner, Matthias</td>
<td>Straße des 17. Juni 135, 10623 Berlin</td>
</tr>
<tr>
<td>Emara, Yasmine</td>
<td></td>
</tr>
<tr>
<td>Lehmann, Annekatrin</td>
<td>E-Mail: <a href="mailto:info@see.tu-berlin.de">info@see.tu-berlin.de</a></td>
</tr>
</tbody>
</table>
# Table of contents

Figures .................................................................................................................................................... III
Tables ..................................................................................................................................................... III
Abbreviations ......................................................................................................................................... IV
Glossary ................................................................................................................................................... V
Acknowledgement .................................................................................................................................. VI

1 Introduction ..................................................................................................................................... 1

2 General Information ........................................................................................................................ 3
  2.1 Validity (temporal and geographic)................................................................................................. 3
  2.2 Conformity with other standards and guidelines.......................................................................... 3
  2.3 Product category and classification............................................................................................... 4
  2.4 Product description ....................................................................................................................... 5
  2.5 Stakeholder participation and communication.............................................................................. 5

3 PCR Review and background information ....................................................................................... 6
  3.1 Existing PCR for the same product category ................................................................................. 6
  3.2 Reasoning for PCR development.................................................................................................... 6
  3.3 Supporting LCA studies ................................................................................................................. 6

4 Goal and scope ................................................................................................................................ 7
  4.1 Goal of the study ............................................................................................................................. 7
  4.2 Functional Unit (FU) ..................................................................................................................... 7
  4.3 Time period .................................................................................................................................... 8
  4.4 Content Declaration ...................................................................................................................... 8
  4.5 Product system ............................................................................................................................... 9
  4.6 General data requirements .......................................................................................................... 12

5 Life cycle inventory ........................................................................................................................ 15
  5.1 Use of primary data ....................................................................................................................... 15
  5.2 Use of secondary data .................................................................................................................... 17
  5.3 Handling data gaps ....................................................................................................................... 20
  5.4 Distribution stage ......................................................................................................................... 25
  5.5 Use stage ..................................................................................................................................... 31
  5.6 End-of-life stage ............................................................................................................................ 35
  5.7 Allocation ................................................................................................................................... 39
  5.8 Biobased Carbon Storage ............................................................................................................. 40

6 Impact assessment ........................................................................................................................ 42
  6.1 Impact categories, indicators and impact assessment models..................................................... 42
  6.2 Optional elements ......................................................................................................................... 43

7 Results and Interpretation ............................................................................................................ 44
  7.1 Results ....................................................................................................................................... 44
  7.2 Interpretation ............................................................................................................................... 45
8  Additional information .................................................................................................................. 46
9  Publication bibliography ............................................................................................................. 47
10  Annex ........................................................................................................................................ 54
10.1  Documents used for PCR development ................................................................................ 54
10.2  Conformity matrix ................................................................................................................. 55
10.3  Data collection sheet ............................................................................................................. 58
Figures

Figure 1: Structure of the PCR for pharmaceutical products and processes ............................................. 2
Figure 2: Generic life cycle of a pharmaceutical product ........................................................................... 10
Figure 3: "Gate" definition within the life cycle of a pharmaceutical product ........................................ 11
Figure 4: Distribution stage of a pharmaceutical product ..................................................................... 25
Figure 5: Use stage of a pharmaceutical product .................................................................................. 32
Figure 6: EoL stage of a pharmaceutical product ................................................................................ 36

Tables

Table 1: Overview of processes that potentially require primary data (depending on the definition of the core system).................................................................................................................................................. 15
Table 2: Overview of processes that potentially require secondary data (depending on the definition of the core system)............................................................................................................................................. 17
Table 3: Approaches to handle data gaps ................................................................................................. 21
Table 4: Process description and modelling approaches (distribution stage) .......................................... 27
Table 5: Process description and modelling approaches (use stage) ....................................................... 33
Table 6: Process description and modelling approaches (EoL stage) .................................................... 37
Table 7: Midpoint impact categories and assessment models for pharmaceutical products and processes.................................................................................................................................................. 42
Table 8: Overview of documents that served as an input to develop the PCR for pharmaceutical products and processes.................................................................................................................................................. 54
Table 9: Conformity matrix PCR ............................................................................................................. 55
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG</td>
<td>Arzneimittelgesetz (medicines law, Germany)</td>
</tr>
<tr>
<td>AoP</td>
<td>Areas of Protection</td>
</tr>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification scheme</td>
</tr>
<tr>
<td>BAT</td>
<td>Best Available Techniques</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstracts service</td>
</tr>
<tr>
<td>CLP</td>
<td>Classification, labelling and packaging of substances and mixtures</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined daily dose</td>
</tr>
<tr>
<td>DQR</td>
<td>Data Quality Rating</td>
</tr>
<tr>
<td>EC</td>
<td>European commission</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EoL</td>
<td>End-of-Life</td>
</tr>
<tr>
<td>EPD</td>
<td>Environmental Product Declaration</td>
</tr>
<tr>
<td>FU</td>
<td>Functional unit</td>
</tr>
<tr>
<td>GWP</td>
<td>Global Warming Potential</td>
</tr>
<tr>
<td>GPI</td>
<td>General Programme Instructions</td>
</tr>
<tr>
<td>HVAC</td>
<td>Heating/Ventilation/Air conditioning</td>
</tr>
<tr>
<td>IES</td>
<td>International EPD® System</td>
</tr>
<tr>
<td>ILCD</td>
<td>International Reference Life Cycle Data System</td>
</tr>
<tr>
<td>IPCC</td>
<td>Intergovernmental Panel on Climate Change</td>
</tr>
<tr>
<td>ISIC</td>
<td>International Standard Industrial Classification</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>LCA</td>
<td>Life cycle assessment</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter</td>
</tr>
<tr>
<td>PCR</td>
<td>Product Category Rules</td>
</tr>
<tr>
<td>PEF</td>
<td>Product Environmental Footprint</td>
</tr>
<tr>
<td>PoE</td>
<td>Point of Emission</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>REACH</td>
<td>Registration, Evaluation, Authorization and Restriction of Chemicals</td>
</tr>
<tr>
<td>Rx</td>
<td>Recipere (lat.), prescription medicine</td>
</tr>
<tr>
<td>SU</td>
<td>Sales unit</td>
</tr>
<tr>
<td>TP</td>
<td>Treatment period</td>
</tr>
<tr>
<td>US EPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>WBCSD</td>
<td>World Business Council for Sustainable Development</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WWTP</td>
<td>Wastewater treatment plant</td>
</tr>
<tr>
<td><strong>Glossary</strong></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Auxiliary material</td>
<td>Material that facilitates the synthesis and feed into the desired product</td>
</tr>
<tr>
<td>Comparative assertions</td>
<td>Published statement about the superiority/equivalence of one product compared to others</td>
</tr>
<tr>
<td>Core system</td>
<td>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</td>
</tr>
<tr>
<td>Desired product</td>
<td>Product (or intermediate) that is the main reason to run a process and which is needed to fulfil the functional unit</td>
</tr>
<tr>
<td>Developer of the study</td>
<td>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</td>
</tr>
<tr>
<td>Healthcare facility</td>
<td>Hospital, nursing home or similar institutions</td>
</tr>
<tr>
<td>Methodological requirements</td>
<td>Rules for a product category to conduct an LCA study or create an Environmental Product Declaration (EPD)</td>
</tr>
<tr>
<td>Operating material</td>
<td>Material that is necessary to run a process but do not feed into the desired product</td>
</tr>
<tr>
<td>Over The Counter-products</td>
<td>Pharmaceutical products which can be purchased without a medical prescription</td>
</tr>
<tr>
<td>Preparation</td>
<td>Final pharmaceutical product</td>
</tr>
<tr>
<td>Primary data</td>
<td>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</td>
</tr>
<tr>
<td>Primary packaging</td>
<td>Packaging that contains the product (direct contact with the preparation)</td>
</tr>
<tr>
<td>Producer</td>
<td>Company that actually produces a pharmaceutical product or input material for pharmaceutical processes</td>
</tr>
<tr>
<td>Rx-products</td>
<td>Pharmaceutical products which require a medical prescription</td>
</tr>
<tr>
<td>Secondary data</td>
<td>Data from commonly available data sources (e.g. databases, proxy/default data)</td>
</tr>
<tr>
<td>Secondary packaging</td>
<td>Packaging that contains one or more packed products (no direct contact with the preparation)</td>
</tr>
<tr>
<td>Summary of product characteristics</td>
<td>Technical information on a pharmaceutical product</td>
</tr>
<tr>
<td>Supporting LCA studies</td>
<td>Studies which are used to develop the PCR</td>
</tr>
<tr>
<td>Tertiary packaging</td>
<td>Packaging for the purposes of transport, handling and/or distribution (no direct contact with the preparation)</td>
</tr>
</tbody>
</table>
Acknowledgement

This publication is part of a project within the initiative for sustainable pharmacy, funded by the German Federal Environmental Foundation (Deutsche Bundesstiftung Umwelt, DBU). We gratefully acknowledge the provided financial support by the DBU and the engagement of the accompanying group of experts:

- Richard Hirsch, TH Köln
- Martin Erhardt and Thorsten Sehl, Herbrand PharmaChemicals
- Dana Kralisch, Friedrich-Schiller University Jena
- Pascal Mielke, Berlin Chemie
- Norbert Möller, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL (Federal Office of Consumer Protection and Food Safety)
- Ines Rönnefahrt, Umweltbundesamt, UBA (Federal Environment Agency)
- Peter Saling, BASF SE
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 ingedients (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 programme 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 scheme² (level II). For this purpose, specific rules are provided³ 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.
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 14025:2011 (Environmental labels and declarations - Type III environmental declarations - Principles and procedures) (ISO 2006a)

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 clearly 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
  UNCP 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.
  - 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.

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

- The “production of \([X] \text{ kg API}\)” or “production of \([X] \text{ DDD of the pharmaceutical product (packed/unpacked)}\)” \((\text{mass-based FU}^{10})\)
  
  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.

\(\square\) 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.

\(\square\) 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\(^\text{13}\). 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\(^\text{14}\) 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 excluded, 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 geographic 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, 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 intended 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 handled 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 future 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>
<thead>
<tr>
<th>Core system</th>
<th>Primary data required</th>
<th>Description</th>
</tr>
</thead>
</table>
| API production       | ▪ Material input (including substrates, reagents, solvents, catalysts and other auxiliary material)  
                       ▪ Operating material  
                       ▪ Energy input  
                       ▪ (Co-)Products  
                       ▪ Waste (solid/liquid)  
                       ▪ Waste water  
                       ▪ Direct emissions to air/soil/water  
                       ▪ Transports | 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)  
                       | Qualitative and quantitative data on the desired product and possible co-products |  
                       | 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)                                      |  
                       | 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
<table>
<thead>
<tr>
<th>Core system</th>
<th>Primary data required</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galenic formulation</td>
<td>▪ Material input (including API, components and other auxiliary material)</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>▪ Operating material</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Energy input</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ (Co-)Products</td>
<td>Qualitative and quantitative data on the desired product and possible co-products</td>
</tr>
<tr>
<td></td>
<td>▪ Waste (solid/liquid)</td>
<td>Qualitative and quantitative data on:</td>
</tr>
<tr>
<td></td>
<td>▪ Waste water</td>
<td>- Production waste and the treatment pathway</td>
</tr>
<tr>
<td></td>
<td>▪ Direct emissions to air/soil/water</td>
<td>- (In-) direct discharge of waste water to municipal WWTP or industrial WWTP (on site), WWTP technology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Direct emissions, exhaust gas cleaning (on site)</td>
</tr>
<tr>
<td></td>
<td>▪ Transports</td>
<td>Qualitative and quantitative data on transport distances, utilization and vehicles for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Transport from (at least) 1st tier supplier to production site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Production waste to treatment plant</td>
</tr>
<tr>
<td>Packaging</td>
<td>▪ Material input (including preparation, packaging components and other auxiliary material)</td>
<td>Qualitative and quantitative data on the preparation, 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)</td>
</tr>
<tr>
<td></td>
<td>▪ Operating material</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Energy input</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ (By-)Products</td>
<td>Qualitative and quantitative data on the desired product and possible co-products</td>
</tr>
<tr>
<td></td>
<td>▪ Waste (solid/liquid)</td>
<td>Qualitative and quantitative data on:</td>
</tr>
<tr>
<td></td>
<td>▪ Waste water</td>
<td>- Production waste and the treatment pathway</td>
</tr>
<tr>
<td></td>
<td>▪ Direct emissions to air/soil/water</td>
<td>- (In-) direct discharge of waste water to municipal WWTP or industrial WWTP (on site), WWTP technology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Direct emissions, exhaust gas cleaning (on site)</td>
</tr>
<tr>
<td></td>
<td>▪ Transports</td>
<td>Qualitative and quantitative data on transport distances, utilization and vehicles for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Transport from (at least) 1st tier supplier to production site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Production waste to treatment plant</td>
</tr>
</tbody>
</table>

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
- Pharmaceutical manufacturer instructions/approval dossiers
- Measurements/experimental data
- Bill of materials (BOM)
- Invoices/economic data (e.g. company's 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)*

<table>
<thead>
<tr>
<th>Upstream/downstream system</th>
<th>Secondary data required</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of precursor chemicals</td>
<td>Material input (including substrates, reagents, solvents, catalysts and other auxiliary material)</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>Operating material</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Energy input</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(By-)Products</td>
<td>Qualitative and quantitative data on the desired product and possible co-products</td>
</tr>
<tr>
<td><strong>Upstream/downstream system</strong></td>
<td><strong>Secondary data required</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>• Waste (solid/liquid)</td>
<td>Qualitative and quantitative data on:</td>
</tr>
<tr>
<td></td>
<td>• Waste water</td>
<td>- Production waste and waste treatment pathway</td>
</tr>
<tr>
<td></td>
<td>• (In-) direct emissions to air/soil/water</td>
<td>- (In-) direct discharge of waste water to municipal WWTP or industrial WWTP (on site), WWTP technology</td>
</tr>
<tr>
<td></td>
<td>• Transports</td>
<td>- (In-) direct emissions, exhaust gas cleaning (on site)</td>
</tr>
<tr>
<td>Distribution stage</td>
<td>• Storage</td>
<td>Qualitative and quantitative data on transport distances, utilization and vehicles for:</td>
</tr>
<tr>
<td></td>
<td>• Waste (solid/liquid)</td>
<td>- Transport from resource extraction to production site, and from there to the next costumer</td>
</tr>
<tr>
<td></td>
<td>• (In-) direct emissions to air/soil/water</td>
<td>- Production waste to treatment plant</td>
</tr>
<tr>
<td></td>
<td>• Transports</td>
<td>Qualitative and quantitative data on energy input (e.g. cooling)</td>
</tr>
<tr>
<td>Use stage</td>
<td>• Additional devices to administer the API</td>
<td>Qualitative and quantitative data on:</td>
</tr>
<tr>
<td></td>
<td>• Energy input (if applicable)</td>
<td>- Waste (unsold/expired products, tertiary packaging) and waste treatment pathway</td>
</tr>
<tr>
<td></td>
<td>• Pharmacokinetic data</td>
<td>- (In-) direct emissions, exhaust gas cleaning (on site)</td>
</tr>
<tr>
<td></td>
<td>• Waste (solid/liquid)</td>
<td>Qualitative and quantitative data on transport distances, utilization and vehicles for:</td>
</tr>
<tr>
<td></td>
<td>• (In-) direct emissions to air/soil/water</td>
<td>- Transport to wholesaler (if applicable), (hospital-) pharmacy(^\text{20}), and from there to the patient</td>
</tr>
<tr>
<td></td>
<td>• Additional devices to administer the API</td>
<td>- Production waste to treatment plant</td>
</tr>
<tr>
<td></td>
<td>• Energy input (if applicable)</td>
<td>Qualitative and quantitative data on the energy input (for cooling and additional devices)</td>
</tr>
<tr>
<td></td>
<td>• Pharmacokinetic data</td>
<td>Qualitative and quantitative data on the pharmacokinetic behavior of the API in the body (e.g. absorption rate) (see also chapter 5.5)</td>
</tr>
<tr>
<td></td>
<td>• Waste (solid/liquid)</td>
<td>Qualitative and quantitative data on:</td>
</tr>
<tr>
<td></td>
<td>• (In-) direct emissions to air/soil/water</td>
<td>- Waste (packaging, additional devices, e.g. single-use syringe, regular and irregular disposal of unused/expired drugs) and waste treatment pathway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Direct emissions of API due to exhalation (if applicable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Other (in-) direct emissions</td>
</tr>
</tbody>
</table>

\(^{20}\) Considering the scope of the PCR, these are the only ways to distribute pharmaceuticals (see §47 AMG)
<table>
<thead>
<tr>
<th>Upstream/downstream system</th>
<th>Secondary data required</th>
<th>Description</th>
</tr>
</thead>
</table>
|                             | 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) | 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) |
|                             | Operating material      | Qualitative and quantitative data on material input (e.g. precipitants) |
|                             | Energy input            | Qualitative and quantitative data on energy input |
|                             | Waste (solid/liquid)    | Qualitative and quantitative data on:
|                             | Waste water             | - Other waste and waste treatment pathway
|                             | (In-) direct emissions to air/soil/water | - (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 Analysys 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/leaflet
- 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 hierarchy (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>
<thead>
<tr>
<th>Data gap</th>
<th>Assumption(^{21})</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| 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, substances 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.
<table>
<thead>
<tr>
<th>Data gap</th>
<th>Assumption</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| 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          | • 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) |
| (e.g. auxiliary material)     |                                                                            |                                                                                                                                                                                                         |                                                                                                |
| Transport distances,          | • 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) |
<table>
<thead>
<tr>
<th>Data gap</th>
<th>Assumption</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrastructure</td>
<td>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</td>
<td>The approach of an average chemical plant by Althaus et al. (2007) can be used if infrastructure is considered</td>
<td>See Althaus et al. (2007)</td>
</tr>
</tbody>
</table>
| 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\textsuperscript{22}:  
\textit{Hazardous waste}: 49% to landfill, 6% to incineration (without energy recovery), 7% to incineration (with energy recovery), 38% recycled  
\textit{Non-hazardous waste}: 48% to landfill, 2% to incineration (without energy recovery), 4% to incineration (with energy recovery), 47% recycled |

\textsuperscript{22} Default values are provided by calculating the average based of data on waste management in the European Union published by Eurostat (2018)
<table>
<thead>
<tr>
<th>Data gap</th>
<th>Assumption</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| (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 excluded. 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](image)

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-)

1 i.e. Hospital ward and pharmacy
2 Including personal pick-up & mail-order
pharmacies or directly administered in a healthcare facility. This shall be clearly defined by the developer of the study. For this purpose, the following approaches should be used:

- **Default approach**: The distribution of the product to the (hospital-) pharmacy (directly or via wholesaler) and purchasing activities of consumers can be modelled by using default data provided in Table 4.

- **Scenario approach**: 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 reveal 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)

<table>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| 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 leaflet. 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 limitation 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.
<table>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage at conventional and hospital pharmacies can be either industrial or household like</td>
<td>Energy demand_{storage} = Specific energy consumption \times \text{Volume}_{Product} \times \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 leaflet or other sources</td>
<td>Specific energy consumption (household like, i.e. fridge-freezer combination): - 1,2 kWh/L/year^{28}</td>
<td></td>
</tr>
<tr>
<td>Foreign pharmacies are not considered due to large differences regarding distribution practices (Campos and Galve 2011)</td>
<td>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)</td>
<td>Average storage time: - 4 weeks (at conventional pharmacy) (PZ 2010) - 3 weeks (at hospital pharmacy) (expert judgement) - 2 weeks (at wholesaler) (expert judgement)</td>
<td></td>
</tr>
<tr>
<td>No cooling during purchasing via mail-order/ personal pick-up can be assumed^{29}</td>
<td>Purchasing distances: - 4-6 km (personal pick-up) (average per federal state according to Neumeier (2013)) - 528-792 km (mail-order)^{30}</td>
<td>Transport on foot and by bicycle are assumed to have no environmental impact</td>
<td></td>
</tr>
<tr>
<td>Transport on foot and by bicycle are assumed to have no environmental impact</td>
<td>Vehicles: - Personal pick-up: Bicycle, car (diesel or petrol, Euro 5, engine size 1,4-2), public transport (bus and/or train)</td>
<td>For personal pick-up: Allocation problems due to other purchases</td>
<td></td>
</tr>
<tr>
<td>For personal pick-up: Allocation problems due to other purchases</td>
<td>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.</td>
<td>Purchasing by the patient via mail-order or personal pick-up from conventional pharmacy (if pharmaceuticals administered at home)</td>
<td></td>
</tr>
</tbody>
</table>

---

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))
<table>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>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.</td>
<td>- Mail-order: Truck (Euro 6, up to 7,5 t) • Mode of transport&lt;sup&gt;31&lt;/sup&gt;: - 22% on foot, 11% by bicycle, 56% by car, 11% by public transport</td>
<td></td>
</tr>
<tr>
<td>Purchasing by the patient via personal pick-up from hospital pharmacy (if pharmaceuticals administered at home)</td>
<td>• Purchasing on foot or by bicycle is negligible due to the distance to hospital</td>
<td></td>
<td>- 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</td>
</tr>
</tbody>
</table>

<sup>31</sup> Based on BMVI (2018); transport mode „car“ includes “MIV Fahrer“ and “MIVMitfahrer“
<table>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| Disposal of transport packaging and unused 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 (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%\textsuperscript{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)\textsuperscript{35}  
  - Unused products: 100% incinerated (with energy recovery)  
  - The incineration takes place 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.

\textsuperscript{32} Expired or unsold; loss rates at consumer are not included in this life cycle stage

\textsuperscript{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)

\textsuperscript{34} Following the recommendations provided by the European Commission for healthcare products (EC 2017)

\textsuperscript{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)\textsuperscript{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 excluded because these processes can not be clearly assigned to the use of pharmaceuticals. The use stage is illustrated by the following Figure 5:

---

\textsuperscript{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.
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>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| 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.                                                                 | -                                                                        |
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 additionally 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)

<table>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| **Regular** disposal of unused pharmaceuticals | • In households, unused pharmaceuticals are disposed of via residual waste or local waste collection points38;  
• 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 separately | 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)                                                                       |
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 excluded 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
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>
<thead>
<tr>
<th>Process</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| 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

<table>
<thead>
<tr>
<th>Regular disposal of unused products</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
</table>
| • For households, unused pharmaceuticals are either disposed of as residual waste or via waste collection points | See Siegert et al. (2019b) | • 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 |
| • 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 |  |  |  |

<table>
<thead>
<tr>
<th>Irregular disposal of unused products (via sinks/toilets)</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• See chapter 5.5 and Siegert et al. (2019b)</td>
<td>(Siegert et al. 2019b)</td>
<td>See Siegert et al. (2019b)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EoL of used/administered pharmaceuticals</th>
<th>Assumptions</th>
<th>Approach</th>
<th>Default data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• See Siegert et al. (2019b)</td>
<td>(Siegert et al. 2019b)</td>
<td>See Siegert et al. (2019b)</td>
<td></td>
</tr>
</tbody>
</table>

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 additionally 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 it 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, stoichiometry 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 economic allocation is used, the developer of the study shall document the economic 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 European 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>
<thead>
<tr>
<th>Impact category (indicator)</th>
<th>Impact assessment model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Climate change (Global Warming Potential GWP)</td>
<td>IPCC model for Global Warming Potential (GWP) over a 100 year time horizon (IPCC 2013)</td>
</tr>
<tr>
<td>Human toxicity (Human Toxicity Potential, cancerogenic / non-cancerogenic)</td>
<td>USEtox model (Rosenbaum et al. 2008; Rosenbaum et al. 2011)</td>
</tr>
<tr>
<td>Ecotoxicity (Freshwater aquatic ecotoxicity potential)</td>
<td>USEtox model (Rosenbaum et al. 2008)</td>
</tr>
<tr>
<td>New pharmaspecific impact categories</td>
<td>New characterization models</td>
</tr>
</tbody>
</table>

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 resources, 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 addressed?

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 internally, 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 clearly 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 analysis52) 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.

\(^{53}\) 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

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.
9 Publication bibliography


Belboom, Sandra; Renzoni, Robert; Verjans, Benoît; Léonard, Angélique; Germain, Albert (2011): A life cycle assessment of injectable drug primary packaging. Comparing the traditional process in glass vials with the closed vial technology (polymer vials). In Int J Life Cycle Assess 16 (2), pp. 159–167. DOI: 10.1007/s11367-011-0248-z.


Cespi, Daniele; Beach, Evan S.; Swarr, Thomas E.; Passarini, Fabrizio; Vassura, I.; Dunn, Peter J.; Anastas, Paul T. (2015): Life cycle inventory improvement in the pharmaceutical sector. Assessment of the sustainability combining PMI and LCA tools. In Green Chem. 17 (6), pp. 3390–3400. DOI: 10.1039/C5GC00424A.


De Soete, Wouter; Dewulf, Jo; Cappuyens, Philippe; van der Vorst, Geert; Heirman, Bert; Aelterman, Wim et al. (2013): Exergetic sustainability assessment of batch versus continuous wet granulation based pharmaceutical tablet manufacturing. A cohesive analysis at three different levels. In Green Chem. 15 (11), p. 3039. DOI: 10.1039/c3gc41185k.


IES (2014): Product Category Rules UN CPC 35270 Vaccines for Human or Veterinary Medicine, whether or not put up as medicaments. The International EPD® System.


Jödicke, Gerald; Zenklusen, Oliver; Weidenhaupt, André; Hungerbühler, Konrad (1999): Developing environmentally-sound processes in the chemical industry: a case study on pharmaceutical intermediates. In Journal of Cleaner Production (7), pp. 159–166.


Lee, Cher Kian; Khoo, Hsien Hui; Tan, Reginald B. H. (2016): Life Cycle Assessment Based Environmental Performance Comparison of Batch and Continuous Processing. A Case of 4- d -


McAlister, Scott; Ou, Yanjun; Neff, Elise; Hapgood, Karen; Story, David; Mealey, Philip; McGain, Forbes (2016): The Environmental footprint of morphine: a life cycle assessment from opium poppy farming to the packaged drug. In *BMJ open* 6 (10), e013302. DOI: 10.1136/bmjopen-2016-013302.


Raju, Geo; Sarkar, Prabir; Singla, Ekta; Singh, Harpreet; Sharma, Rachit Kumar (2016a): Comparison of environmental sustainability of pharmaceutical packaging. In Perspectives in Science 8, pp. 683–685. DOI: 10.1016/j.pisc.2016.06.058.


Ramasamy, Sri Vaitheki; Titchener-Hooker, Nigel J.; Lettieri, Paola (2015): Life cycle assessment as a tool to support decision making in the biopharmaceutical industry. Considerations and challenges. In Food and Bioproducts Processing 94, pp. 297–305. DOI: 10.1016/j.fbp.2014.03.009.


van der Vorst, Geert; Aelterman, Wim; Witte, Bruno de; Heirman, Bert; van Langenhove, Herman; Dewulf, Jo (2013): Reduced resource consumption through three generations of Galantamine-HBr synthesis. In Green Chem. 15 (3), p. 744. DOI: 10.1039/c3gc36854h.

van der Vorst, Geert; Dewulf, Jo; Aelterman, Wim; Witte, Bruno de; van Langenhove, Herman (2011): A systematic evaluation of the resource consumption of active pharmaceutical ingredient production at three different levels. In Environmental science & technology 45 (7), pp. 3040–3046. DOI: 10.1021/es1015907.

van der Vorst, Geert; van Langenhove, Herman; Paep, Frederik de; Aelterman, Wim; Dingenen, Jules; Dewulf, Jo (2009): Exergetic life cycle analysis for the selection of chromatographic separation processes in the pharmaceutical industry. Preparative HPLC versus preparative SFC. In Green Chem. 11 (7), p. 1007. DOI: 10.1039/b901151j.


### 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))

<table>
<thead>
<tr>
<th>Type of document</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic standards and guidelines</td>
<td>- ISO 14025 (ISO 2006a)</td>
</tr>
<tr>
<td></td>
<td>- ISO 14040/44 (ISO 2006b, 2006c)</td>
</tr>
<tr>
<td></td>
<td>- ISO TS 14027 (ISO 2017)</td>
</tr>
<tr>
<td></td>
<td>- Guidance for Product Category Rule Development (GPCRD) (GPCRD 2013)</td>
</tr>
<tr>
<td></td>
<td>- Product Environmental Footprint Category Rules Guidance (PEFCRG) (EC 2017b)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sector-specific guideline</th>
<th>GHG Protocol Product Life Cycle Accounting and Reporting Standard (NHS 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices (NHS 2015)</td>
</tr>
<tr>
<td></td>
<td>Life Cycle Metrics for Chemical Products (WBCSD 2014)</td>
</tr>
</tbody>
</table>

| Existing PCR            | PCR for Vaccine for human or veterinary medicine, whether or not put up as medicaments (IES 2014) |

### 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Introduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 General Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 Validity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 Conformity w other standards &amp; guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 Product category &amp; classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 Product description</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 Stakeholder participation &amp; communication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------</td>
<td>--------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>3 PCR review &amp; background information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Existing PCR for the same product category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 Reasoning for PCR development</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3 Supporting LCA studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Goal &amp; scope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 Goal of the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2 Functional Unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.3 Time period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.4 Content declaration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5 Product system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.6 General data requirements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 LC Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1 Use of primary data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2 Use of secondary data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------</td>
<td>------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>5.3 Handling data gaps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4 Distribution stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5 Use stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.6 End-of-life stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.7 Allocation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.8 Biogenic Carbon Storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 Impact assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1 Impact categories, indicators &amp; impact assessment models</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.2 Optional elements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7 Results &amp; interpretation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1 Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2 Interpretation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>8 Additional Information</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 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 disposal
  - 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