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Environmental assessment model for pharmaceutical products

Environmental risks related to Active Pharmaceutical Ingredients (API) and carbon footprint in a life cycle perspective

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In cooperation with The Research-Based Pharmaceutical Industry (LIF)

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Summary

Pharmaceutical products have an impact on the environment along the life cycle, from extraction of resources, through processing, production and transportation stages to use and end of life. To be able to assess and evaluate the environmental consequences of pharmaceutical products, reliable, comparable and relevant information is needed about the environmental impacts along the life cycle.

The objective of this project is to develop and propose a model for environmental assessment of pharmaceutical products in a life cycle perspective, in regard to environmental risks related to emissions of Active Pharmaceutical Ingredient (API) and product carbon footprint. The model is intended to facilitate comparability of performed assessments of products with the same API and allow for third party review and validation, to ensure credibility and quality of reported results. Thus, the project addresses two key environmental challenges for the pharmaceutical industry - environmental risks associated with emissions of API and climate change. Other environmental impacts have been excluded from the project, but the assessment model can be expanded to include additional risk factors and other relevant environmental impact categories at a later stage.

The proposed environmental assessment model consists of two parts;

- Environmental risk assessment (ERA) of emissions of API from local production.
- Carbon footprint of pharmaceutical products in a life cycle perspective.

The two parts supplements and expands the current environmental classification at Fass.se, which covers environmental risks from release of API from patient excretion in Swedish water recipients.

The proposed ERA part of the model builds on the current environmental classification at Fass.se, where some calculations have been updated to reflect local emissions from production rather than emissions after use. The model includes the stages of the life cycle where API can be/is released to the environment; in the production of the API, and in the formulation and packaging of the pharmaceutical products. Emissions from patient excretion is already covered by the current classification.

The carbon footprint part of the model covers greenhouse gas emissions in a life cycle perspective. To secure comparability and verifiability, we propose to use the framework described in ISO 14025 for environmental product declarations and initiate the development of Product Category Rules (PCR) for pharmaceutical products. A PCR describes and harmonizes scope and content for what to include in data collection, calculations and reporting for a specific product category. A modularised set-up for the PCR development is proposed, building on earlier harmonization efforts and experiences with life cycle assessments and carbon footprints within the pharmaceutical industry.

The proposed model is aimed to deliver product specific environmental assessment results that may be used in a wide variety of different applications to control, manage and reduce impacts along the pharmaceutical value chain and drive improvements in different parts of the chain. The report includes an overview of potential use of the information by different stakeholders, such as pharmaceutical benefits subsidy systems, procurement, process and product improvement, guidance in product choice as well as assessments in conjunction with product approval.

The actual intended application of results, however, needs to be better understood in order to prioritise and guide further development and implementation of the model. Therefore, we propose the following main areas for further development:

Clarify needs, requirements and use of product specific environmental information for pharmaceuticals; by different stakeholders along the pharmaceutical value chain and for different applications. This should include a stakeholder mapping and analysis to define where and how the information can be used to drive improvements in different parts of the chain, including drivers, incentives and barriers.

Continue harmonization, development and implementation of the proposed model in the pharmaceutical business, based on identified stakeholder requirements and intended applications. Areas for further development of the model is outlined in the report and includes e.g. establishing PCR development and identifying needs for supporting guidelines and tools to facilitate data collection, calculations and reporting, defining synergies and communication of results from the model as a whole (environmental risk and carbon footprint) as well as deciding where to start implementation based on requirements and feasibility.

Sammanfattning

Läkemedelsprodukter har en påverkan på miljön under hela sin livscykel: från utvinning av råmaterial, genom bearbetnings- och produktionssteg, vid transporter och slutligen vid användning och sluthantering av produkten. För att kunna bedöma och utvärdera miljökonsekvenser av läkemedelsprodukter krävs tillförlitlig, jämförbar och relevant information om miljöpåverkan längs produkternas hela livscykler.

Syftet med detta projekt är att utveckla och föreslå en modell för miljöbedömning av läkemedelsprodukter i ett livscykelperspektiv, med avseende på miljörisk vid utsläpp av API (aktiv läkemedelssubstans) och klimatavtryck för produkt. Modellen är avsedd att underlätta jämförelser av utförda miljöbedömningar för produkter med samma API. Den ska även möjliggöra tredjepartsgranskning och validering, för att säkerställa trovärdighet och kvalitet i rapporterade resultat. Projektet adresserar alltså två viktiga miljöutmaningar för läkemedelsindustrin – miljörisker kopplade till utsläpp av API och klimatförändringar. Projektet omfattar inte annan miljöpåverkan utöver dessa två områden, men bedömningsmodellen kan utökas i ett senare skede till att inkludera ytterligare riskfaktorer och fler relevanta miljöpåverkanskategorier.

Den föreslagna miljöbedömningsmodellen består av två delar:

- Miljöriskbedömning av utsläpp av API (aktiv läkemedelssubstans) från lokal produktion av läkemedel.
- Klimatavtryck av läkemedelsprodukter i ett livscykelperspektiv.

De två delarna kompletterar och utvidgar den befintliga miljöklassificeringen på Fass.se, som omfattar miljöriskerna av de API som når svenska vattenrecipienter genom utsöndring från patienter.

Den föreslagna miljöriskdelen av modellen bygger på den nuvarande miljöklassificeringen på Fass.se, där vissa beräkningar har uppdaterats för att spegla lokala utsläpp från produktion snarare än utsläpp efter användande av läkemedel. Modellen innefattar de stadier i livscykeln där det finns en risk att API kan släppas ut i miljön; vid produktion av API och vid sammansättning och paketering av läkemedelsprodukten. Utsläpp till följd av utsöndring från patient täcks redan av nuvarande klassificering.

Den del av modellen som avser klimatavtryck omfattar utsläpp av växthusgaser i ett livscykelperspektiv. För att säkerställa jämförbarhet och verifierbarhet föreslår vi att ramverk för miljövarudeklarationer som beskrivs i ISO 14025 bör användas och att utveckling av PCR (produktspecifika regler) för läkemedelsprodukter initieras. En PCR beskriver och harmoniserar innehåll och omfattning gällande vad som ska inkluderas vid datainsamling, beräkningar och rapportering för en specifik produktkategori. En modulariserad struktur föreslås för utvecklingen av PCR, som bör bygga på tidigare harmoniseringsinsatser och erfarenheter av livscykelanalys och klimatavtryck inom läkemedelsindustrin.

Den föreslagna modellen levererar produktspecifika resultat från miljöbedömningar som kan användas på en mängd olika sätt för att kontrollera, styra och reducera miljöeffekter längs värdekedjan för läkemedel, och för att driva förbättringsarbete i olika steg i kedjan. Rapporten innefattar en översikt av potentiella användningsområden för denna information av olika intressenter; såsom i system för läkemedelsförmåner, upphandling, process- och

produktförbättringar, guidning vid produktval samt bedömningar i samband med godkännande av produkt.

För att styra fortsatt utveckling och implementation av modellen behöver dock de faktiska avsedda tillämpningarna av modellen bättre förstås. Vi föreslår därför följande områden för fortsatt utveckling:

Klargör behov, krav och användning av produktspecifik miljöinformation för läkemedel; för olika intressenter längs värdekedjan och för olika tillämpningar. Detta bör inkludera en kartläggning och analys av intressenter för att definiera var och hur informationen kan användas för att driva förbättringsarbete i olika delar av kedjan, inklusive drivkrafter, incitament och hinder.

Fortsätt harmonisering, utveckling och implementering av den föreslagna modellen i läkemedelsindustrin, baserat på identifierade intressentbehov och avsedda tillämpningar. Områden för fortsatt utveckling beskrivs i rapporten och inkluderar t.ex. att etablera utveckling av PCR; att identifiera behov av stödjande riktlinjer och verktyg som underlättar datainsamling, beräkningar och rapportering; att definiera synergier och kommunikation av resultaten från hela modellen (miljörisk och klimatavtryck) samt att besluta var man ska börja implementation baserat på krav och genomförbarhet.

1 Introduction

There is an increased focus and awareness of the environmental consequences of pharmaceuticals. The use of pharmaceuticals is growing globally, and the number of pharmaceutical products is increasing. The positive effects of pharmaceuticals in terms of improved health and well-being for pharmaceutical users, however, also have negative effects in terms of impacts on the environment. The occurrence of pharmaceutical substances in both water and environment is increasing, and there is a growing number of bacteria resistant to antibiotics.

So far much of the attention has been directed towards the environmental consequences of emissions of active pharmaceutical ingredients (API) in different parts of the life cycle, both regarding emissions associated with residues reaching the environment subsequent to human ingestion and excrement, and emissions from production of the APIs.

There is, however, a growing awareness that also other environmental aspects along the pharmaceutical life cycle should be considered, such as climate impacts, resource depletion and other local environmental impacts. In the global business arena, it is starting to be a norm to consider environmental and sustainability aspects along the entire value chain. It is no longer sufficient to only focus on own direct environmental impacts, businesses are expected to take responsibility for indirect impacts upstream in the supply chain, at suppliers and sub suppliers, and downstream in use and end of life of delivered products. This applies also to the pharmaceutical business. A study published by the National Agency for Public Procurement shows that 14 per cent of the climate impacts from Swedish county council purchases emanates from purchasing of pharmaceuticals, pharmacy goods and medical equipment. In individual county councils the share could be substantially higher[1].

A number of studies and strategies have been published highlighting the need for common models and criteria to assess, report and evaluate the environmental impacts of pharmaceutical products, in order to be able to prioritize and promote actions to control and reduce the impacts. In 2011 the Swedish National Pharmaceutical Strategy (NPS) published a list of objectives to minimize the environmental impact of pharmaceuticals[2]. In the interim report from the governmental Pharmaceutical and Pharmacy Inquiry year 2013, one of the recommendations was that TLV (The Dental and Pharmaceutical Benefits Agency) and/or the MPA (Medical Products Agency) should be commissioned to evaluate if and how green economic incentives could be implemented in the generic substitution system[3]. In the same year LIF delivered a proposal for an environmental assessment model to the Ministry of Health and Social Affairs (MHSA), developed in collaboration with Swedish stakeholders and international pharmaceutical industry experts. In the NPS action plan of 2016-2018[4], LIF had the responsibility to further develop the proposed model and evaluate its feasibility and applicability.

[1] Upphandlingsmyndigheten Landstingens miljöpåverkan, Accessed 2019-02-14 https://www.upphandlingsmyndigheten.se/verktyg/statistik-om-offentlig-upphandling/miljospendanalys/landstingens-miljopaverkan

[2] Den nationella läkemedelsstrategin 2011–2018, https://lakemedelsverket.se/overgripande/Om-Lakemedelsverket/Nationell-lakemedelsstrategi/

[3] Ersättning vid läkemedelsskador och miljöhänsyn i läkemedelsförmånerna, Statens offentliga utredningar, SOU 2013:13

[4] Nationella läkemedelsstrategin 2016–2018, Regeringskansliet, S2015/08203/FS

In June 2018 the Swedish Medical Products Agency published an action plan that outlines how the Agency will contribute to the Swedish environmental goals and Agenda 2030[5]. In the plan, six overarching measures have been identified, based on a life cycle perspective for pharmaceutical products:

- Increase environmental considerations in permitting licenses for pharmaceuticals
- Improve knowledge and reduce exposure of substances that are harmful to the environment
- Promote availability of environmental information for pharmaceuticals in a concerted manner
- Reduce discharges of environmentally harmful substances from production of pharmaceuticals
- Reduce environmental impacts in use of pharmaceuticals, medical/technical products and cosmetic products
- Stimulate development of pharmaceutical products with low overall environmental impact

Also, the Swedish Government has given the Swedish Medical Products Agency the mandate to establish and be responsible for a Competence Center for Pharmaceuticals as a part of the activities at the Agency[6]. The center starts in 2019 and the following areas have been specifically observed as future focus areas for the activities in the center[7]:

- Strengthen the knowledge of pharmaceutical substances of being environmentally harmful
- Increase capacity-building about sustainable manufacturing
- Develop criteria for environmental assessment

According to the Swedish Medical Products Agency environmental criteria can be used for several purposes such as within the system of substitutable pharmaceuticals, for public procurement of pharmaceuticals, for selling OTC pharmaceuticals and for voluntary initiatives by companies.

A common denominator to support the actions and establish environmental criteria is availability and accessibility of reliable, comparable and relevant information, describing the environmental impacts of production, use and end-of-life of pharmaceutical products. Still, there is a lack of common accepted methods and tools to achieve this.

This project was initiated as a response to this need of information, to develop and show how environmental aspects in production of pharmaceutical products can be acquired, verified and reported, to allow for comparison of environmental performance between different products with the same active pharmaceutical ingredient (API). This may be used as basis for defining specific environmental criteria for different applications, such as procurement.

The project is a further development of the Swedish environmental classification of pharmaceutical substances at Fass.se, which is based on environmental risk assessments (ERAs) of individual active pharmaceutical ingredients (APIs), in terms of emissions from patient excretion in Swedish aquatic environments. The system has been running in Sweden since 2005 and was a response to an increasing political and public demand for environmental information on pharmaceuticals. The system was developed by a Swedish Working Group consisting of the Swedish association of the

[5] Handlingsplan för hur läkemedelsverket fram till 2020 ska verka för att nå miljömålen (reviderad), Läkemedelsverket juni 2018.
[6] Kunskapscentrum för läkemedel i miljön. Verksamhetsplan 2019 – 2023. Läkemedelsverket, december 2018
[7] Uppdrag angående Kunskapscentrum för läkemedel i miljön. Redovisning av regeringsuppdrag. Läkemedelsverket, december 2018

research-based pharmaceutical industry (LIF), the Stockholm county council, the pharmacy chain Apoteket, the Swedish association of local authorities and regions (SKL) and the Swedish Medical Products Agency, in conjunction with the international pharmaceutical industry. The results from the classification are publicly available at Fass.se, a web based pharmaceutical portal that includes information on all approved pharmaceuticals on the Swedish market.

2 Objectives and scope of project

The objective of the project is to develop and propose a model for environmental assessment of production of pharmaceuticals, that includes environmental risks related to emissions of API and climate impacts in terms of carbon footprint for pharmaceutical products in a life cycle perspective. The model should:

- Facilitate comparability between performed assessments of products with the same active pharmaceutical ingredient (API)
- Allow for third party review and validation, to ensure credibility and quality of reported results

The overall ambition is that the model developed and proposed in the project can be used to extend the current environmental classification at the FASS system of pharmaceutical products, to also include environmental classification of the production.

The aim was also to compile first draft recommendations that can be used as input for development of general environmental criteria applicable to the pharmaceutical industry at large, including green economic incentives within the generic substitution system.

The project contributes to several Sustainable Development Goals (SDG) and targets within Agenda 2030, particularly:

- *Goal 6 Ensure availability and sustainable management of water and sanitation for all*, with focus on improving water quality by minimizing release of hazardous substances (target 6.3)
- *Goal 12 Ensure sustainable consumption and production patterns,* with focus on environmentally sound management of chemicals throughout the life cycle (target 12.4), encouraging companies to adopt sustainable practices and integrate sustainability reporting into their reporting cycle (target 12.6), promote sustainable public procurement practices (target 12.7), and ensure that people everywhere have access to relevant information for sustainable development (target 12.8)
- *Goal 13 Take urgent action to combat climate change,* with focus on integrating climate change measures in policies and strategies (target 13.2)
- *Goal 14 Conserve and sustainably use the oceans, seas and marine resources for sustainable development,* with focus on preventing and reduce marine pollution of all kinds (target 14.1)
- *Goal 17 Partnerships for the goals,* with focus on encouraging and promoting public-private partnerships (target 17.17).

Limitations
The scope of the project is pharmaceuticals for human use. However, the model proposed by the project may also be applicable for other related product groups such as veterinary medicine.

Communication of the environmental assessment results have not been included in the project in terms of e.g. content and communication formats. Communication should be adapted to its intended use, and therefore additional guidelines will be needed to define how results can be communicated in an understandable and clear manner to different stakeholders and intended audiences.

In terms of environmental impacts, only climate change and environmental risks related to emissions of API were agreed to be included, as they are key environmental challenges for the pharmaceutical business.

Environmental risks related to emissions of API from different parts of the pharmaceutical life cycle are included as this is becoming a global concern. It is a prioritized area for EU as shown by the Commission´s Strategic Approach to Pharmaceuticals in the Environment ("PiE Strategy")[8]. Pharmaceutical residues in the environment is also a prioritized area within environmental surveillance and within ERA as well as a focus area in the EU Strategy for the Baltic Sea Region, and it is being investigated in a number of national and international projects. In this project, as well as in the current environmental classification at the FASS system, the ERA is based on the EMA guideline[9]. It was not within the scope of the project to further develop the risk assessment methodology. This means that some known environmental risk factors are not included, such as risks for promoting antibiotic resistance in the environment. Also, environmental risks related to emissions of substances other than API from the manufacturing of pharmaceuticals are not included.

Climate change is included as this is a global issue where there is an urgent need for action, emphasized by the Paris Agreement and IPCCs special report published in October 2018 which states that "limiting global warming to 1.5°C would require rapid, far-reaching and unprecedented changes in all aspects of society"[10]. Also, carbon reporting was agreed as a reasonable starting point in terms of availability of data. Many pharmaceutical companies report greenhouse gas emissions in their sustainability reports, and thus some of the needed data is already acquired. Other environmental impact categories such as water use, acidification, eutrophication, resource use etc. are not included.

The assessment model should be possible to expand to include other relevant environmental risk factors and impact categories at a later stage.

[8] European Union Strategic Approach to Pharmaceuticals in the Environment. http://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF
[9] EMA guideline 2006, European Medicine Agency. Committee for Medicinal Products for Human use (CHMP): Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CPMP/SWP/4447/00. London (UK): EMA 12 p.
[10] IPPC Special report - Global Warming of 1.5 ºC. https://www.ipcc.ch/sr15

3 Overview of the parts in the environmental assessment model

The environmental assessment model developed in the project consists of two main parts:

- environmental risk management and assessment of the local emissions of API in production process steps - described in chapter 4
- carbon footprint of pharmaceutical products in a life cycle perspective – described in chapter 5

The two parts of the model supplements each other in addressing key environmental challenges for the pharmaceutical business - environmental risks from emissions of API and climate change through emissions of greenhouse gases along the life cycle. They are intended to complement the current environmental classification for emissions of API at a national level as performed today, described in the *FASS guideline*[11]. An outline of the scope and content of the different parts is illustrated in Figure 1.

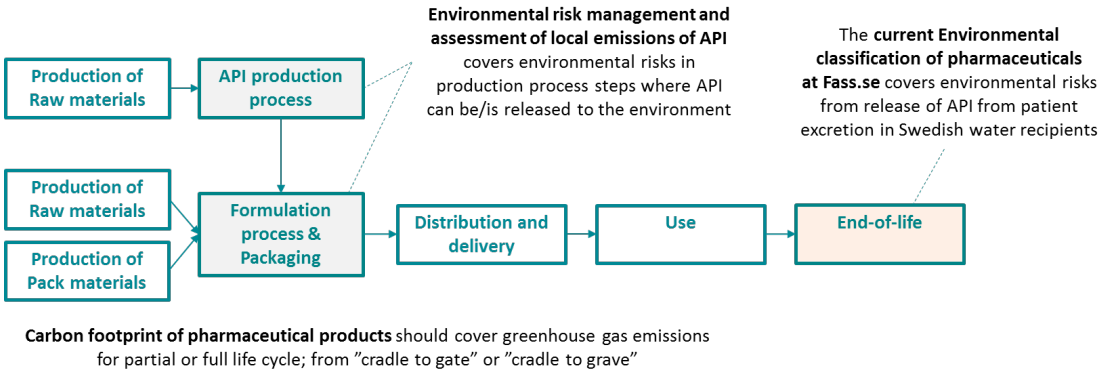

Figure 1. Overview of the different parts of the model and their relations

The model has a potential to be used by different stakeholders along the pharmaceutical value chain for different applications. An overview and introduction to potential use of the model is therefore discussed in chapter 6.

Note: Both parts of the model involve a life cycle perspective for pharmaceutical products, but we have selected different methods for the two parts of the model as indicated above;

- environmental risk assessment (ERA) methodology is used for the local emissions for API and,
- life cycle assessment (LCA) methodology is used for emissions of greenhouse gas emissions and climate impacts.

We have decided not to use LCA methodology for emissions of API, as ERA methodology will provide a more local and representative assessment of the environmental risks compared to what

[11] FASS guideline - Environmental classification of pharmaceuticals at www.fass.se. Guidance for pharmaceutical companies. (2012) http://www.fass.se/pdf/Environmental_classification_of_pharmaceuticals-120816.pdf

is possible with LCA as performed today. The impact assessment in LCA is generally not specific for a local area, and available impact assessment methods also lack assessment factors for many APIs. Because of this, there would be a lot of data gaps.

3.1 About the development of the model

The development has been guided by the overall aims for the project and the model, i.e. that the model should enable comparisons of products with the same API and that results shall be verifiable to enable third party quality assurance of the information to secure that it has been compiled in accordance with the agreed model.

The development has been performed in an interdisciplinary team at IVL, representing expertise in environmental risk assessment, life cycle assessment, environmental product declarations, green public procurement, corporate environmental management and industrial environmental informatics.

During the project, discussions and interviews have been held with representatives from different pharmaceutical companies, to get a better understanding of current status, opportunities and challenges in collecting, compiling and reporting product specific environmental information, and to get input on the proposed assessment models and way forward. The following companies have actively contributed in these discussions: AstraZeneca, Bayer, GSK, Mylan and Pfizer.

Also, the project has had a reference group consisting of different stakeholders to the pharmaceutical business. The following organizations have participated in the reference group: The Research-Based Pharmaceutical Industry (LIF) and the Association for Generic Pharmaceuticals and Biosimilars (FGL) in Sweden, the Swedish Pharmacy Association, The National Agency for Public Procurement, Stockholm County Council, The Swedish Environmental Protection Agency, The Dental and Pharmaceutical Benefits Agency (TLV) and Gothenburg University as well as the pharmaceutical companies mentioned above.

3.2 Types of environmental criteria

Since one of the aims of the environmental assessment model is that it should be possible to use as basis for environmental criteria, an initial screening was made of environmental criteria that is currently used in different applications.

Basically, two main types of criteria have been identified:

- *Management related aspects* – qualitative assessment of systematic way of working to manage and control environmental aspects and risks
- *Performance related aspects* – quantitative assessment of environmental impacts, which can be further subdivided into
    - organizational environmental performance and
    - product environmental performance

Approaches and criteria focused on *management related aspects* typically involve evaluation of the company´s strategy, policies and procedures for managing environmental aspects and risks, including roles and responsibilities, follow-up (such as measurement, monitoring and auditing) as

well as continuous improvements and management of corrective actions. They are usually based on management system principles and standards such as ISO 9001 and ISO 14001. Examples of such initiatives are the procurement criteria proposed by the procurement organization for hospitals in Norway (see further information in chapter 4.1), as well as the code of conduct and follow-up in the Pharmaceutical Supply Chain Initiative (PSCI)[12].

Performance related aspects typically involve ability to deliver quantitative environmental performance data - for the organization and/or its products. Performance data can concern impacts within direct control of the company, i.e. impacts from own production sites, but it can also involve indirect impacts upstream and downstream in the supply chain. Examples of standards and tools for reporting *organizational performance* are the quantitative indicators in Global Reporting Initiative (GRI), the Greenhouse Gas protocol corporate standard and the CDP platform (formerly named Carbon Disclosure Project). Examples of standards and tools for reporting *product performance* are life cycle assessment (ISO 14040/44), environmental product declarations (ISO 14025) and the product standard in Greenhouse Gas protocol. In addition, the pharmaceutical industry has taken a few initiatives to harmonize product performance calculations, such as the NHS guideline and different screening tools. Further information on these standards and tools is available in chapter 5.1.

Regarding environmental criteria used in procurement, most is focused on management related aspects, probably because they are based in general management system principles, and as such there are well-established methods and tools to verify and evaluate compliance in terms of e.g. self-assessments and audits. Performance related aspects in terms of follow-up of quantitative performance for organization or product, is generally not included. This may be due to the fact that such information can be more difficult to verify and evaluate, and thus requires a different set-up for validation and verification compared to management related aspects.

As there already are several initiatives for the management related aspects, the focus for the development in this project has been on product performance in terms of how environmental impacts along the pharmaceutical life cycle can be quantified and reported. The results can form basis for defining future environmental criteria for performance related aspects in different applications (see also discussion in chapter 6).

It should be noted that depending on the application and use of environmental criteria, a combination of both management and performance related aspects may be needed, to get a full understanding of the status, both in terms of how the supplier manages environmental aspects in a systematic way, as well as actual environmental performance and quantitative results for the organization and/or its products. The quantitative information about environmental performance can in this way be seen as proof that management of environmental aspects delivers measurable and tangible results.

[12] PSCI Pharmaceutical Supply Chain Initiative. https://pscinitiative.org/home

3.3 The pharmaceutical business and value chain

The pharmaceutical industry faces a strict regulation which leads to tough competition among companies. Pharmaceuticals are either medicines being prescribed by physicians or sold directly to consumers as so-called "over-the-counter" medicines (OTC). Within these categories, there are three main types of pharmaceuticals on the market – original pharmaceuticals, generic pharmaceuticals and parallel-imported pharmaceuticals:

Original pharmaceuticals, also known as brand-name pharmaceuticals, are still being protected by patents. They are researched, developed, manufactured and sold by research-based pharmaceutical companies. Both API and products are manufactured in-house by the pharmaceutical companies and the supply chain is often quite linear. The original-producing companies have to protect their intellectual properties which is needed to avoid insights from other parties into their manufacturing processes. These processes play an important role in research and development of new products and the companies need to keep their specific knowhow to themselves to maintain a competitive edge.

Generic pharmaceuticals are copies of brand-name drugs, which usually become available where the patents have expired. They are produced and sold by both generic pharmaceutical companies and research-based pharmaceutical companies. The supply chain is usually more complex, including sub-suppliers of APIs and semi-finished products.

Parallel-imported pharmaceuticals are original products produced by pharmaceutical companies in other EU member states. They are imported and sold by the producing companies but also, to some extent, by dealers. The supply chain for parallel-imported pharmaceuticals starts with the purchase of existing pharmaceuticals and consists mainly of re-packaging. The parallel trade is driven by price differences on the market, where the business case is to buy pharmaceuticals in a country where the price is lower and re-package and sell them in another country at a higher price. The parallel trade is mainly focused on original pharmaceuticals with larger margins to make a profit.

The distribution of pharmaceuticals is divided between different actors. The companies producing the pharmaceutical products usually deliver them to pharmaceutical wholesale-companies. The wholesale-companies further distribute the products to retailers (e.g. local pharmacies, hospitals etc.), from which they are handed over or sold to patients.

Many raw materials and products are often traded on global scale where the supply chain may be long and complex, with suppliers located all over the world. For example, for pharmaceuticals sold in the Swedish market, a major part of the APIs originates from Asia, see Figure 2. In some of the countries, environmental policy measures that controls emissions is not fully developed, as indicated by the Environmental Performance Index in Figure 2. The index is developed and maintained jointly by Yale University and Columbia University in collaboration with the World Economic Forum and ranks 180 countries on 24 performance indicators across ten issue categories covering environmental health and ecosystem vitality[13].

[13] Environmental Performance Index. https://epi.envirocenter.yale.edu/

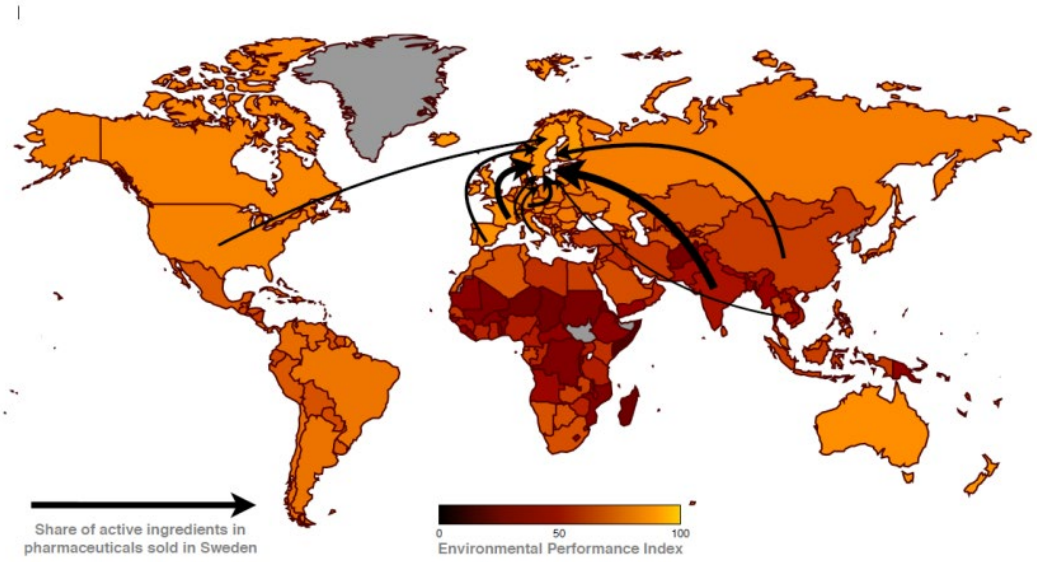

Figure 2. An illustration of the dominant flows of trade of APIs in pharmaceutical products in a global context[14]

The complexity of the supply chains poses specific challenges in acquiring and reporting information about the environmental impacts in different parts of the value chain. It can be difficult to get information from suppliers, especially beyond the first-tier supplier, and issues with confidentiality often hamper exchange of information. For product specific environmental information, the information may be especially sensitive as it may include company internal information about the specific production processes in terms of e.g. use of materials, waste and yield.

[14] Bengt-Palme, J., Gunnarsson, l. and Larsson, D.G.J. (2017) Co-branding and price of pharmaceutical guide informed choices towards informed pollution control during manufacturing. Journal of Cleaner Production 2017-09.

4 Environmental risk assessment - emissions of active pharmaceutical ingredients from local production

The model for local environmental assessment of API emissions from production consists of:

- Part 1. Information about environmental risk management adopted from Norway (Sykehusinnkjöp).
- Part 2. Local environmental risk assessment of emissions of API.

The two parts of the model provide a qualitative evaluation of management related aspects for how the reporting company works with risk management in a systematic way, and a quantitative evaluation of the performance of API production in terms of environmental risk, based on an ERA. The evaluation results in a characterisation of the local environmental risk in production of a specific API.

The local environmental risk assessment of emissions of API focuses on the parts of the life cycle where API can be/is released to the aquatic environment, as indicated in Figure 3, i.e. in the production of API, in the formulation and packaging, as well as after use. The focus of this project is the production parts, whereas emissions after use (indicated as "end-of-life" in the figure) is already covered by the current environmental classification at Fass.se.

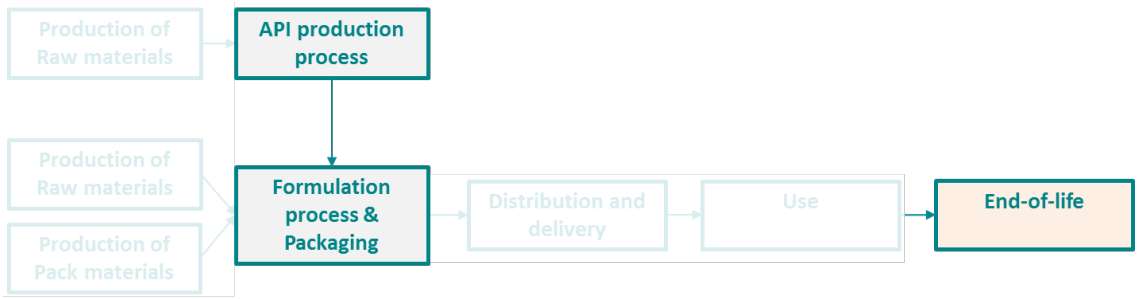

Figure 3. Overview of the parts of the life cycle where API can be/is released to the aquatic environment

The model for local emissions in production is introduced in the following subchapters, and can be found in full in Appendix I, including data requirements for the local environmental risk assessment as well as an outline for a guideline and a calculation example.

In the development of the calculation model for the local environmental assessment of emissions of active pharmaceutical ingredients, the current classification model at Fass.se has been used as starting point, but some calculations have been altered to reflect local emissions from production rather than emissions after use.

4.1 Part 1. Environmental risk management

Part 1 of the model involves a qualitative assessment of the supplier's level of risk management, in terms of policies, procedures and follow-up. The procurement organization for hospitals in Norway (Sykehusinnkjöp) has proposed questions regarding environmental risk management to be used with pharmaceutical suppliers in future tenders, see part 1 in Appendix I. At the time of writing, the questions have been tested in one tender. As the set of questions provide an overview of different key aspects in environmental risk management, we have chosen to adopt these as basis for the overall environmental risk evaluation. We have adopted these questions as they are, without any change or further adaptation, in order to harmonize within the Nordic countries and facilitate for the companies which will provide the information. This will allow the same answers to be reused for this purpose.

The evaluation of the responses will result in a qualitative score for the company´s level of environmental risk management. The evaluation could for example be done in a scale from "no systematic risk management" to "excellent/best in class risk management". We aim to align also the evaluation with the model for evaluation defined by the procurement organization in Norway. They have defined a price premium up to a certain percentage which is based on the result from evaluation of the company´s response, and in this way provide an incentive for companies to report.

4.2 Part 2. Local environmental risk assessment of pharmaceutical emissions

In addition to the questions regarding the suppliers' environmental risk management we want to include more information about the emissions from the production. This is done in order to be able to perform ERA on local API emissions from the production sites, which will enable comparison of APIs from different manufacturers in a quantitative manner.

The proposed model is based on the current environmental classification as it is performed today for Fass.se, which includes emissions after use in Swedish water recipients. The current environmental classification, review process and model are briefly introduced in section 4.2.1 and 4.2.2. The proposed model for emissions of API from local production sites is introduced in section 4.2.3. Some limitations with the proposed model are also discussed in section 4.2.4.

4.2.1 Current environmental classification and review process

The current Swedish environmental classification guidance document[15] is based on the European Medicines Agency (EMA) guideline for ERA of pharmaceutical substances[16] and the European

[15] FASS guideline - Environmental classification of pharmaceuticals at www.fass.se. Guidance for pharmaceutical companies. (2012) http://www.fass.se/pdf/Environmental_classification_of_pharmaceuticals-120816.pdf

[16] EMA guideline 2006, European Medicine Agency. Committee for Medicinal Products for Human use (CHMP): Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CPMP/SWP/4447/00. London (UK): EMA 12 p.

Commission Technical Guidance Document[17]. In the Swedish environmental classification of pharmaceutical substances, the risk posed by the individual API is differentiated into four categories: i) insignificant risk; ii) low risk; iii) moderate risk and iv) high risk. In addition to the environmental risk phrase, each API is assigned hazard phrases for persistence and bioaccumulation. A substance can be exempted from classification, in accordance with the EMA guideline[18], if they are unlikely to result in significant risk to the environment, e.g. vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids.

The environmental classification system is a self-declaration system meaning that each pharmaceutical company is responsible for reported environmental information. The pharmaceutical companies compile and provide the information in accordance with the guideline, and an external independent party, the Swedish Environmental Research Institute, IVL, is reviewing the classifications to evaluate that they are based on a scientifically acceptable interpretation of the guideline. In the reviewing process the reviewing team at IVL comment on the proposed classification based on the data provided by the companies and gives recommendations to LIF whether or not revision is required before publication. The exchange of information is done in a web-based application, developed by IVL in cooperation with LIF.

The environmental assessment at Fass.se is presented at two different levels. For the non-expert user there is a level with summary phrases describing the classifications regarding environmental risk, degradation and bioaccumulation, assigned to the substance. For the expert reader a second level includes all information that has been submitted as basis for the self-declaration, including a list of references to documents that have been used.

4.2.2 Current model for classification – emissions from patient excretion in Swedish water recipients

The current calculation model that the ERA is based on uses the predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC). The PEC and PNEC are used to calculate a risk characterization ratio (RCR), which corresponds to one of the above mentioned four risk categories. The API is then assigned a risk phrase which corresponds to the risk category.

The PEC is calculated using a formula that uses total actual API sales (active moiety) in Sweden for the most recent year, removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation), the number of inhabitants in Sweden, the volume of waste water per capita and day and a factor for dilution of waste-water by surface water flow.

The PNEC value is ideally based on ecotoxicological data from three trophic levels (usually algae, crustaceans and fish). The PNEC should preferably be obtained by applying assessment factors (AF) to long-term ecotoxicity data in accordance with the ECHA guidance[19] If long-term data is lacking, short-term ecotoxicity data may be used. An AF of 1000 is normally applied to the most sensitive of three short-term toxicity endpoints. However, the AF may be reduced to 100, 50 or 10,

[17] European Commission, European Chemicals Bureau. (2003) Technical Guidance Document on Risk Assessment.
[18] EMA guideline 2006, European Medicine Agency. Committee for Medicinal Products for Human use (CHMP): Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CPMP/SWP/4447/00. London (UK): EMA 12 p.
[19] ECHA, European Chemicals Agency. (2008) Guidance on information requirements and chemical safety assessment.

depending on the number of long-term NOEC (No Observed Effect Concentration) endpoints available, providing long-term data are available for the species with the lowest acute value.

In-depth details regarding the calculation model can be found in the FASS guideline[20].

4.2.3 Proposed model for classification – local emissions from production

The calculation model for the ***local*** environmental risk assessment of emissions of API from production, proposed in this project, differs from the current assessment model only in the PEC calculation, which has been updated to reflect local emissions of API at the production site, instead of after-use emissions. The other parts of the assessment are done in the same way as the current classification, where the PNEC part is based on the EMA guideline for environmental risk assessment[21], see subsection 4.2.2 for further details.

The new PEC, termed PEC_{local}, is based on local emission of API into the recipient, removal rate in sewage treatment facilities, waste-water volume through which API is released to the environment, and a dilution factor by which the waste-water is diluted in the recipient. The calculation model is explained in detail in Part 2 in Appendix I. Environmental risk.

Local emissions of API can occur from different manufacturing process steps, such as in the production of the API and in the formulation process and packaging. Emissions from all relevant process steps should be included. If more than one production site is involved in the production at different locations, the result for each location should be reported. The resulting environmental classification is then the location with the highest risk.

4.2.4 Delimitations in the proposed model

There are a number of limitations in the proposed model that may lead to underestimation of the risks:

In this method it is not taken into account that more than one facility in the same area may produce identical APIs and release to the same water recipient, which would lead to underestimation of the concentration.

Another limitation of the model is that the current assessment is based on the potential risk posed by single substances rather than the combinations of substances, and combination effects (mixture toxicity) may therefore be overlooked or underestimated.

Toxicological studies for the calculation of PNEC are often performed with animals used in standardized methods. Ideally, the test organisms should represent organisms from the local recipient since they may be more or less sensitive than the animals in the standardized methods. However, toxicological studies are expensive and the European medicines agency (EMA) does not demand this proceeding. Also, the assessment factors (AF) used in the calculation provide a

[20] FASS guideline - Environmental classification of pharmaceuticals at www.fass.se. Guidance for pharmaceutical companies. (2012) http://www.fass.se/pdf/Environmental_classification_of_pharmaceuticals-120816.pdf

[21] EMA guideline 2006, European Medicine Agency. Committee for Medicinal Products for Human use (CHMP): Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CPMP/SWP/4447/00. London (UK): EMA 12 p.

margin of safety for extrapolation between species. Therefore, PNEC can be calculated as described in the FASS guideline.

Ideally the dilution factor should be calculated for the specific water recipient and water flow at the time for disposal, and companies are encouraged to do so, if they have the possibility. However, it can be difficult and expensive to perform such measurements properly. Therefore, when specific data is not available, a country average dilution factor has initially been decided to be sufficient for the calculation, based on Keller et al. (2014)[22].

Another limitation of the model is that it only includes risk factors that are covered by the EMA guideline. This means that some known environmental risk factors are not included, such as risks for promoting antibiotic resistance in the environment. This should be an area for further development.

4.3 Recommendations for further development and implementation

The two parts of the proposed model have been discussed with representatives for pharmaceutical companies. Regarding part 1 of the model, all agree that harmonizing evaluation of environmental risk management within the Nordic countries will facilitate information sharing. Regarding part 2 of the model, the companies have assessed that it is possible to acquire the data for local emissions which is needed to perform the updated risk calculations, and that the information may be presented to the review team. Thus, the proposed PEC_{local} calculation model may be included in the FASS guideline[23] and in the reviewing process that is already running today. Some further development is, however, needed before implementation can start, as outlined below.

Additional pilot tests should be performed to secure that data collection and reporting can be performed in an equivalent manner by different companies. It should be recognised that the possibility to acquire and verify the data needed for the PEC_{local} calculation can differ greatly depending on the reporting company´s operational or financial control of the production. When the production processes are owned/within control of the reporting company, it is generally feasible to acquire the data needed for the calculation. Data for the different included parameters may then already be available within internal information systems, as part of internal environmental risk assessment procedures. But when the API production and/or formulation and packaging is performed by a supplier or sub-supplier, the possibility to acquire and verify data can be restricted due to e.g. confidentiality reasons. This should to be evaluated and addressed in further development, including need for supporting tools to facilitate data collection. See also corresponding discussion concerning supplier data collection in section 5.3.

The model is based on emissions of API from production sites in different parts of the life cycle. A production site may produce an API which is subsequently used in the production of several different products. A production site may also perform formulation of several products which include the same API. Further development is needed to clarify how the risk classification for the

[22] Keller, V.D.J., et al. Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors. (2014) Environmental Toxicology and chemistry. Vol 33, no 2 447-452. https://setac.onlinelibrary.wiley.com/doi/epdf/10.1002/etc.2441

[23] FASS guideline - Environmental classification of pharmaceuticals at www.fass.se. Guidance for pharmaceutical companies. (2012) http://www.fass.se/pdf/Environmental_classification_of_pharmaceuticals-120816.pdf

production sites should be assigned on individual product level. This needs to be defined and agreed within the industry.

The procedure for review and verification of reported information also needs to be further developed and should be aligned with review procedures for the carbon footprint part (see chapter 5). Due to confidentiality reasons, it is recommended that only the classifications that result from the PEC_{local} calculations should be disclosed at Fass.se and that second-level information, i.e. the detailed background information and calculations, is only disclosed to the review team. The second-level information allows third party verification of the information, but as it includes detailed information about localisation and emissions from production which usually is internal information and not disclosed publicly, it needs to be up to the reporting company to decide whether to share any additional background information.

Based on this, the following steps are proposed in order to further develop and later on implement the local ERA into the FASS system:

- Harmonise data collection for PEC_{local}, to secure that data can be collected in an equivalent manner by different companies by performing pilot tests. The pilot tests will also provide input to development of a guideline for the model.
- Define how risk classification results for production sites on API level should be assigned on individual pharmaceutical product level.
- Define procedure for review and verification based on results from the pilot tests, securing alignment with procedures for verification for the carbon footprint part (chapter 5).
- Update the FASS guideline to include the proposed model and review procedure for local ERA
- Develop the FASS-web-application which is used for communication between supplier and review team, to include local ERA in order to facilitate review of submitted data.
- Define and decide how the information should be presented and communicated at Fass.se in an understandable manner.

Additional environmental risk factors, that are not yet included in the EMA guideline, should also be taken into consideration in the further development. At least criteria for antibiotics and endocrine disruptors should be included in the model to cover for the risks of antibiotic resistance and endocrine disorders.

5 Carbon footprint of pharmaceutical products in a life cycle perspective

The background, basis and proposal for carbon footprint assessment of pharmaceutical products in a life cycle perspective are described in the following subchapters.

The life cycle perspective involves consideration of environmental impacts along the full life cycle of a product or a service, from extraction of raw materials, through all processing, production and transport stages to the use and final end-of-life of the product. In Figure 4, the life cycle for a pharmaceutical product is schematically illustrated. It includes extraction, production and transport of raw materials and packaging materials used in the product, production of the API and formulation and packaging of the pharmaceutical product as well as distribution. It also includes delivery of the product by e.g. pharmacies, the administration and use of the product by pharmaceutical users, and final end-of-life through disposal of the product and packaging. In each stage of the life cycle, materials and energy are used, waste is generated, and different substances may be emitted to air, water and soil.

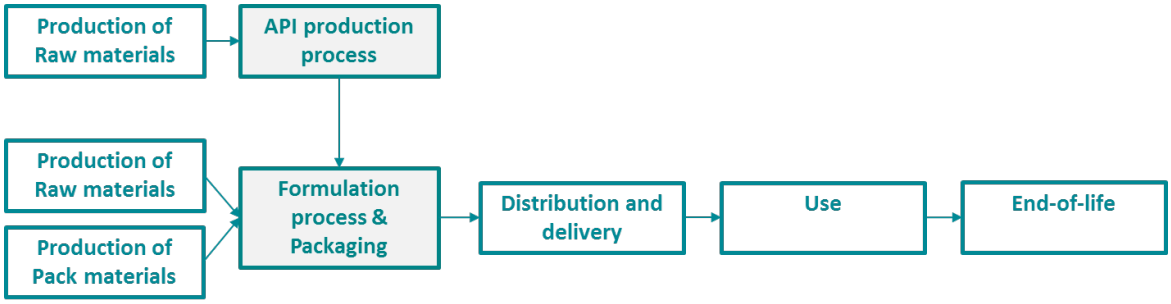

Figure 4. Schematic illustration of the life cycle of a pharmaceutical product

An overview of relevant available standards and tools for environmental assessments in a life cycle perspective is given in chapter 5.1, including how they are currently used in the pharmaceutical industry.

Based on the review of standards, we propose to use the framework described in ISO 14025 for environmental product declarations as basis for developing life cycle-based carbon footprints for pharmaceutical products. ISO 14025 is based on the standards for life cycle assessment (LCA) as described in ISO 14040/44. They form a solid foundation for the assessment, as they are well established standards, developed to facilitate comparable, transparent communication of verified LCA results. They are widely applied in different industries, and for different applications such as in Green Public Procurement (GPP).

As part of this framework, Product Category Rules (PCR) is defined, which in detail describes and harmonizes scope and content for what to include in data collection, calculation and reporting for a specific product category. Therefore, we propose to establish a PCR for pharmaceutical products, utilizing earlier harmonization initiatives and experiences with life cycle assessments and carbon footprints within pharmaceutical companies. The proposal is described in chapter 5.2. Some opportunities and challenges in developing a PCR and carbon footprint reporting for pharmaceutical products is further discussed in chapter 5.3.

It should be noted that this part of the project has only focused on performance related environmental aspects in terms of carbon footprint (as discussed in chapter 3.2). Contrary to the environmental risk part, no management related aspects are included, e.g. in terms of questions concerning how the company manages environmental aspects, as this was not the focus of the project. However, it is recommended that such criteria should be based on the international standard for environmental management systems, ISO 14001, as this provides a common framework for managing environmental aspects in a systematic way[24]. With the updated version launched in 2015, this standard also includes requirements on considering a life cycle perspective. Also, industry initiatives such as the Pharmaceutical Supply Chain Initiative (PSCI)[25] should be considered, to evaluate if the environmental part could be further developed to enhance environmental improvement work in the pharmaceutical supply chain and facilitate collection and sharing of environmental data.

5.1 Overview of standards for environmental assessment in a life cycle perspective and use in the pharmaceutical industry

There are a number of standards and tools available for product environmental assessments and product carbon footprints in a life cycle perspective. They are briefly described below, including how they are currently used within the pharmaceutical business.

5.1.1 Quantify environmental impacts along the life cycle – Life cycle assessment (LCA)

Most life cycle-based methods and tools are based on the international standards for life cycle assessment, ISO 14040 and ISO 14044[26]. These standards describe the framework for performing life cycle assessment (LCA), and requirements for the different phases in the work - how to define goal and scope, how to collect and compile environmental data for the studied system (referred to as inventory), how perform environmental impact assessment as well as how to interpret the results. General requirements regarding reporting and verification are also included. LCA is a well-established method applied in many different industries and for a range of different applications, such as product development, strategic planning, marketing and communication.

Several of the participating pharmaceutical companies have long experience in performing and applying life cycle assessments for internal use, to both improve the general knowledge of the products and to guide strategic and operational decisions in process and product development. For example, results are used to identify opportunities for process improvements, to support selection of packaging materials, or to follow-up the results from changes that have been implemented in the life cycle for the product.

[24] ISO (2015) Environmental management systems – Principles with requirements for use. ISO 14001:2015, Geneva
[25] PSCI Pharmaceutical Supply Chain Initiative. https://pscinitiative.org/home
[26] ISO (2006) Environmental management – Life cycle assessment – Principles and framework. ISO 14040: 2006 and ISO (2016) Environmental management – Life cycle assessment – Requirements and guidelines. ISO 14044:2016, Geneva

With a few exceptions, it is unfortunately not common to disclose or make the results publicly available. Among the reasons for not to publish results may include confidentiality issues which hampers the possibility for full transparency of the study and results, or that the studies have been made for a specific goal and scope and therefore results are not comparable or relevant to disclose to the public. Studies for a similar product performed by different companies may have been done with a different goal and scope, where methodological choices, choice of data, etc. may differ, which quite naturally lead to differences in the results. For example, process steps or materials may have been omitted in the study, which affect the total end results. Also, there may be a fear that results could be misinterpreted and misused, as LCA results always needs to be interpreted and understood a professional way and in line with the goal and scope.

Most companies are performing LCA for specific products and applications, and generally not for their full product portfolio. One pharmaceutical company estimated that of the total assortment for the Swedish market, they have performed LCA on about 10 per cent of these products. Thus, it may be difficult to deliver environmental information for a full product assortment on a specific market, as the information is not readily available, and therefore would require additional new studies to be performed.

5.1.2 Communicating LCA results and footprints

Results from LCAs can be communicated in many different ways, using different formats. ISO 14025 was developed to both establish a common way to conduct comparable LCA studies and define how to report the results[27]. It is based on LCA according to ISO 14040/44 and describes specific requirements for compilation and reporting of comparable, transparent, and third-party verified information about the life-cycle environmental impact of products, in the form of Environmental Product Declarations, EPD (referred to as Type III environmental declarations). The standard also specifies system and administrative requirements for EPD program operators that register EPDs and maintains a publicly available library of EPDs and Product Category Rules (PCR). One such system is the International EPD® System[28].

A central element in the EPD framework is PCR, which specifies detailed requirements for how the LCA shall be performed for a specific product category. These rules are intended to ensure transparency and comparability of results for the product category, as they regulate methodological choices and data requirements when performing the LCA. Development of PCRs is described in a specific technical specification, ISO/TS 14027[29], in which one key requirement is that the development shall be made in a transparent and open participatory process in a global context, where interested parties for the product category have the possibility to actively participate. This also includes an open international consultation, where all relevant stakeholders can comment on the PCR proposal. The aim of the process is to reach consensus in the relevant business sector, and consequently the whole PCR set-up is intended to provide acceptance and buy-in of the resulting PCR document.

[27] ISO (2006) Environmental labels and declarations - Type III environmental declarations - Principles and procedures. ISO 14025:2006, Geneva
[28] The International EPD® System. www.environdec.com
[29] ISO (2017) Environmental labels and declarations – Development of product category rules. ISO/TS 14027, Geneva, 2017

EPDs are used in different applications, such as green public procurement (GPP) and building assessment schemes. EPDs have been published for a wide range of product groups, such as building products, food, hygiene products, etc.

EPDs has, however, so far not been used in the pharmaceutical industry, with one exception. In 2012, an EPD for the veterinary vaccine Improvac® was published by Zoetis Inc. in the International EPD® System. As basis for the EPD, a PCR was developed and published for the product group "Vaccines for human or veterinary medicine, whether or not put up as medicaments"[30]. Note: The EPD has been de-registered by the company and are therefore no longer available.

On EU level, a similar initiative as EPD was started in 2011, named Product Environmental Footprint (PEF)[31]. The initiative was initiated to enable a single market for green products within the EU and is partly based on the ISO standards mentioned above but includes additional detailed specifications. In the same way as ISO 14025, PEF is also built on product category rules, named PEFCR. The method has been pilot tested for several product groups, such as decorative paints, a number of food products, footwear, batteries and accumulators, and is now in a transition phase where the commission will evaluate the pilot tests and decide further use of the method within the EU. Work is currently ongoing in evaluating how the EPD framework and PEF may be aligned.

5.1.3 Carbon footprint reporting

In addition to the standards described above, there are a number of standards relating specifically to carbon footprint accounting and reporting. Such are sometimes referred to as a "single-issue LCA" or "single-issue EPD".

Among the most widely used is Greenhouse Gas (GHG) protocol, developed and maintained in partnership between World Resources Institute (WRI) and the World Business Council for Sustainable Development (WBCSD)[32]. GHG protocol is the basis for reporting greenhouse gas emissions in accordance with GRI (Global Reporting Initiative) and in the CDP platform (formerly named Carbon Disclosure Project).

GHG protocol has both a corporate standard[33] and a product life cycle standard[34]. In the corporate standard, reporting is divided into three scopes:

- *Scope 1 Direct GHG emissions*, which occur from sources that are owned or controlled by the company
- *Scope 2 Electricity indirect GHG emissions*, which accounts for GHG emissions from the generation of purchased electricity consumed by the company
- *Scope 3: Other indirect GHG emissions*, which are a consequence of the activities of the company but occur from sources not owned or controlled by the company. Examples of scope 3 activities are extraction and production of purchased materials; transportation of purchased fuels; and use of sold products and services.

[30] PCR 2011:11 Vaccines for human or veterinary medicine (expired), International EPD® System, https://www.environdec.com/PCR/Detail/?Pcr=7848
[31] Single Market for Green Products Initiative, European Commission, http://ec.europa.eu/environment/eussd/smgp/index.htm
[32] GHG protocol, https://ghgprotocol.org/
[33] A Corporate Accounting and Reporting Standard, GHG Protocol, https://ghgprotocol.org/corporate-standard
[34] Product Life Cycle Accounting and Reporting Standard, GHG Protocol, https://ghgprotocol.org/product-standard

Several pharmaceutical companies publish sustainability reports which include data for carbon emissions compiled according to the GHG protocol, and they also report in the CDP platform. Some pharmaceutical companies are reporting indirect scope 3 emissions along their value chain. However, it is usually difficult to compare reported data as organizational scopes differs between different companies. This means that what is included in the reporting of scope 1, scope 2 and scope 3 respectively differs depending on the organizational boundaries for the specific companies. Also, scope 3 reporting is optional, and there is a large flexibility in terms of what categories to include in the reporting. For example, some may only report emissions from transportation, whereas others may report emissions from their entire supply chain in production of purchased goods and services.

Two ISO standards have been published with similar scopes as Greenhouse gas protocol, specifically focused on carbon accounting and reporting. These are ISO 14064 which describes organizational reporting[35] and ISO/TS 14067 which describe product reporting[36]. An advantage with the ISO standards is that they are aligned with other environmental management standards in the ISO family, and thus ISO/14067 build on the requirements in ISO 14025 and ISO 14040-44. These ISO-standards are used in some industries, but the GHG protocol still remains as the most applied standard for corporate greenhouse gas accounting and reporting.

5.1.4 Pharmaceutical specific guidelines and tools for product environmental assessments

Over the years the pharmaceutical industry has taken several initiatives regarding product environmental assessments and carbon footprint. These are briefly introduced below:

NHS guideline for product carbon footprint assessment

In 2012, a guideline was developed and published to enable consistent carbon footprint assessments for products[37]. The guideline is based on the product life cycle standard in GHG protocol and was developed by the National Health Service (NHS) in UK in collaboration with different stakeholders, including representatives for several pharmaceutical companies, Government and health care providers. The document contains guidance for defining system boundaries, i.e. what process steps to include in the reporting and what processes that may be excluded, as well as guidance for data collection and data quality assessment. Detailed guidance is given for defining the product system for typical process routes for API manufacture and delivery mechanisms.

The guideline however explicitly states that it is not intended for product comparisons, in terms of comparative assertions between products, or claims of favorable environmental performance of one product over another. Some additional specification and requirements are needed, in terms of e.g. specific scope and content as well as data requirements, in order to allow for such comparisons.

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[35] ISO 14064 -1: 2006. Greenhouse gases – Specification with guidance at the organizational level for quantification and reporting on greenhouse gas emission and removal. ISO, Geneva, 2006

[36] ISO/TS 14067: 2018. Greenhouse gases – Carbon footprints of products – Requirements and guidelines for quantification. ISO, Geneva, 2018

[37] Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices, November 2012, https://www.sduhealth.org.uk/areas-of-focus/carbon-hotspots/pharmaceuticals.aspx

Screening tools for product environmental assessments

Two screening tools have also been developed to enable and facilitate for pharmaceutical companies to perform simple product environmental assessments based on product specifications:

The American Chemical Society (ASC) Green Chemistry Institute (GCI) Pharmaceutical Roundtable has developed a simple Excel-tool which allows for estimation of life cycle environmental impacts based on product specification and different process routes, combined with generic data for different raw materials from the Ecoinvent LCA database[38]. The tool presents the result for 6 impact indicators, including greenhouse gas emissions, acidification, eutrophication as well as resource, water and energy use.

The Association for the British Pharmaceutical Industry (ABPI) also distribute a footprint tool, developed by Carbon Trust with contributions from several pharmaceutical companies[39]. The aim of the tool is to provide a quick approximation of the carbon impacts of pharmaceutical tablets in blister packs, specific to the UK pharmaceutical market. The calculation is based on input data for product and packaging specification, as well as some operational inputs like waste generation and transport distances. The tool contains default carbon footprint data for APIs based on statistical assessment of 29 APIs, where the result can be used as an average or divided into Low/Medium/High carbon impact. There is however no detailed information or guidance on what types of APIs that fall in each level of carbon impact. The tool also includes data for a number of excipients.

Both of these screening tools are useful to improve awareness and understanding of environmental and carbon impacts of pharmaceutical products along the life cycle. But they are not intended for product comparison as they are primarily based on generic information and generally do not produce company and product specific results. They can therefore not be directly used to enable comparison between pharmaceutical products with the same API.

5.2 Proposal: Harmonization of reporting through Product Category Rules (PCR) for pharmaceuticals

To secure comparability and transparency of carbon footprint reporting of pharmaceutical products, requirements and scope for reporting needs to be agreed and well defined, i.e. results should be compiled and reported in the same way, independent of company. Results should also be verifiable, to secure that the agreed reporting requirements have been followed.

Therefore, we propose to start from the well-established international standard for environmental product declarations ISO 14025, as this is the only standard that fulfils these pre-requisites. As the scope of this project is carbon footprint, this would constitute a "single-issue" declaration, i.e. the declaration includes only one environmental impact category. We recommend using ISO 14025 as basis, rather than one of the available product carbon footprint standards (ISO 14067 or GHG

[38] ASC GCI Pharmaceutical Roundtable: Process Mass Intensity - Life Cycle Analysis (PMI-LCA) Tool (only available for members) https://www.acs.org/content/acs/en/greenchemistry/industry-roundtables/pharmaceutical.html
[39] ABPI blister pack carbon footprint tool. http://www.abpi.org.uk/what-we-do/research-medical-and-innovation/sustainability

protocol product standard), as this will allow the flexibility to expand the reporting to include other relevant impact categories at a later stage.

As described in chapter 5.2.1, ISO 14025 requires Product Category Rules (PCR) which:

- Specifies rules and requirements for how to perform the LCA (life cycle assessment) for a specific product category. The product category should relate to the function of the product, i.e. the same functional unit may be applied to the products within the category.
- Enables transparency and comparability between products within the same product category
- Is developed in an open process, in cooperation between actors and stakeholders in the product category

Thus, we propose to harmonize reporting through development of a PCR for pharmaceutical products. The general set-up and structure for PCR development is described in chapter 5.2.1. For the development of the PCR we propose a modularized set-up, see further details in chapter 5.2.2. This will both enable a modularized development and agreement on data requirements and calculation rules for different parts of the life cycle, as well as modularized reporting on different levels. To demonstrate how a PCR for a pharmaceutical product may look like, a PCR "embryo" has been developed based on the proposed modularization, see Appendix II.

In the development of the PCR, earlier harmonization initiatives should be utilized, such as the guideline developed by NHS as well as experiences in the pharmaceutical companies in performing product environmental assessments. Another project with partly overlapping objectives has also been running in parallel to this project; the German SERUM research project led by the Technical Universität Berlin (TU Berlin) and funded by the German Federal Environment Foundation. The project started in June 2016 and will end in May 2019. It includes both development of product category rules for pharmaceutical processes and products as well as development new impact assessment (LCIA) methods to consider pharma-specific impacts that is missing in current LCIA methods. The PCR part of this project focus on detailed methodological issues in performing LCA on pharmaceutical products[40]. In further development, the approach proposed in this project should be combined with the approach proposed by the SERUM project, to achieve a broader international consensus, acceptance and agreement.

5.2.1 Process and options for PCR development

Based on requirements in ISO/TS 14027, the general process for PCR development consists of different steps, as outlined in Figure 5.

Figure 5. Overview of the steps involved in developing a PCR.

In the first step of the process (step 1), the work is initiated and planned. A PCR committee is formed, which has the task to develop the content of the PCR. The PCR committee should include

[40] Siegert, M-W., Lehmann, A., Emara, Y. and Finkbeiner, M. (2018) Harmonized rules for future LCAs on pharmaceutical products and processes. Int. J. Life Cycle Assessment, November 2018, pp 1-16

technical expertise for the product category as well as expertise on LCA. Relevant interested parties are also informed that PCR work has started. Interested parties may include:

- Representatives for the supply chain of the product category, such as material suppliers, manufacturers and trade associations
- Representatives for the use of the product category, such as purchasers, users and consumers
- Other organizations such as non-governmental organizations (NGOs), public agencies and, when relevant, independent parties and certification bodies.

In step 2 the draft PCR is developed together with the PCR committee. This involves defining and agreeing on the detailed rules for how to perform the LCA for the specific product category.

The next step (step 3) is open consultation, where a draft PCR document is submitted to representatives of relevant interested parties for feedback. Comments received in the open consultation are handled in the PCR committee and may involve adjustments of the PCR draft into a final document.

The final step (step 4) is approval and publication, where the document is approved and made publicly available.

As things may change over time, the PCR document should be reviewed at a regular frequency and978-91-7883-085-5 be updated when needed. If updating is needed, the update of the document follows the same process as for new PCR development (step 1-4).

Options for PCR development – in existing EPD program or independent

There are basically three main options for organizing PCR development:

- Connect to an existing EPD program
- Establish a new EPD program
- Only utilize parts of the ISO 14025 framework

The usual approach when starting PCR development is to connect to an existing EPD program operator, such as the International EPD ® System, and develop the PCR within the framework specified by the selected program operator. A program operator has generally defined more detailed specifications and requirements for developing and maintaining PCRs and EPDs which is valid for the specific program, based on the requirements in ISO 14025 and ISO/TS 14027. Such specifications include content and scope of the PCRs, general methodological principles which shall be applied e.g. concerning allocation and which impact categories to include, as well as specification of rules for communication and communication formats.

Another potential option is to start PCR and EPD development independently, as a new program. This allows for more flexibility in developing the PCR and in developing reporting principles which can be directly adapted to the specific intended applications. For example, there are EPD programs which are specifically dedicated to construction products. Developing a new program will, however, require decisions and additional development for how such a program should be managed and financed, in addition to the PCR development.

A third potential option is to only utilize parts of ISO 14025 framework, in terms of the principles and procedures to agree on requirements and calculation rules in a PCR, but not go the whole way towards environmental product declarations in an established or new EPD program. This would

allow for full flexibility in development and reporting and could be a way to get started in the pharmaceutical business. When more experiences are gained, the business may at a later stage decide to connect to an existing EPD program or create a new program.

The two latter options may be established as an addition and further development of the current set-up for environmental risk classification, which is maintained in collaboration between LIF and IVL.

Decision will be needed on option and set-up for PCR development

Thus, as part of starting PCR development for pharmaceutical products, a decision should be taken in pharmaceutical business on which route to go as outlined above, i.e. connect to an existing system, start independently or only utilize parts of ISO 14025 as basis.

In terms of forming an PCR committee, it should consist of representatives of the pharmaceutical companies and supply chain, utilizing the experiences and existing internal studies that have been performed, as well as international research results. Interested parties to be invited in open consultation should include key stakeholders such as pharmacies, county councils, and governmental authorities.

It is strongly recommended to handle this as an international effort, to secure that the same requirements and calculation rules can be used on different markets.

5.2.2 Proposed modularized set-up of PCR for pharmaceutical products

We propose a modularized approach for defining and developing a PCR for pharmaceutical products, where the life cycle is divided into three levels with different scopes as indicated in Figure 6:

- *Level 1. Cradle to gate API*: Production of API, including extraction, processing, production and transportation of raw materials.
- *Level 2. Cradle to gate pharmaceutical product*: Formulation and packaging of finished pharmaceutical product, including extraction, processing, production and transportation of raw materials and packaging materials, as well as Level 1 Cradle to gate API.
- *Level 3 Cradle to grave pharmaceutical product*: Full life cycle for pharmaceutical products, includes distribution and delivery, use and end-of life, as well as Level 2 Cradle to gate pharmaceutical product.

Some methodological choices and requirements will apply for all levels of reporting. Therefore, we also propose to define general principles and rules which is valid for all three levels, concerning e.g. allocation and data quality, as well as requirements for processes that is included in all parts of the life cycle, such as energy generation, transportation and waste management.

The modularized set-up of reporting can facilitate compilation of the information, when e.g. the API production and the formulation is done by different companies. Then the company responsible for formulation may request data from its API supplier(s), compiled and independently reviewed in accordance with the level 1 requirements. Level 2 reporting may then be compiled using level 1 results from suppliers. This may be a way to handle confidentiality issues that may hamper sharing of environmental information between companies in the life cycle.

Note: the levels build on each other, i.e. level 1 is a subset of level 2, and level 1 and level 2 are subsets of level 3.

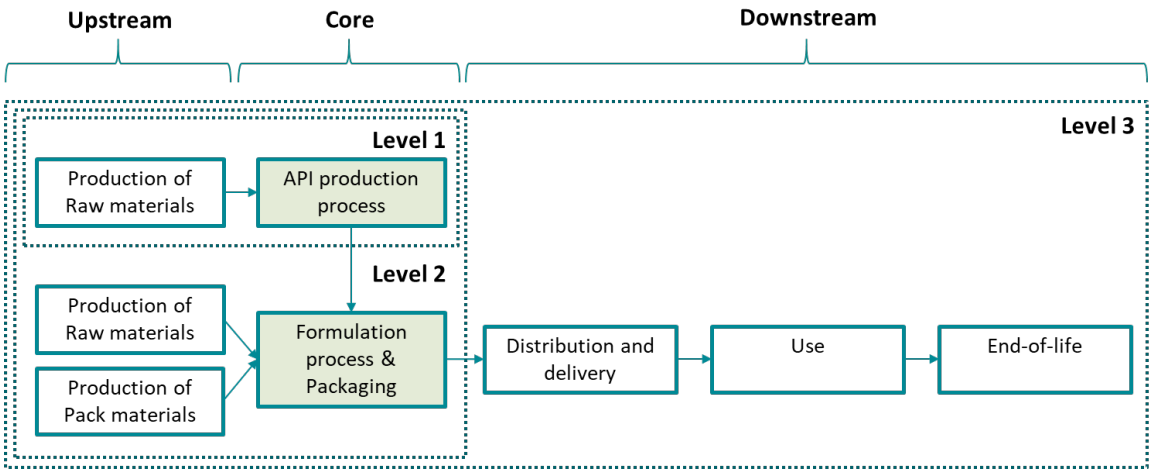

Figure 6. Proposed modularisation of the life cycle of a pharmaceutical product

In keeping with general PCR conventions, the life cycle has also been divided into Upstream, Core and Downstream phases, as indicated in Figure 6. This division is useful both to define specific data requirements and for presentation of results. Usually site and supplier specific data is required for the Core part of the product system, as this represents the part of the product system where the product is produced, whereas generic data, such as industry averages or international databases, can be used for the Upstream part in the supply chain, for production of the materials needed to produce the product. The downstream part may be specific or generic depending on the specific use and end-of-life case for the product.

Grouping of pharmaceutical products and definition of product category

A PCR is based on a well-defined definition of a product category, taking into account e.g. the function of the specific product category. Further development will be needed to define relevant product categories for the reporting levels (1-3) proposed above. For example, the German SERUM project has proposed the third level of the Anatomic Therapeutic Chemical (ATC) classification system as basis for defining product categories, but they also highlight that further specification will be needed as the third level leads to over 300 subcategories[41].

As part of defining product category also a functional unit is defined, i.e. the reference unit for which results shall be reported. As a starting point we propose to use the following functional units for each level of reporting:

- *Level 1. Cradle to gate API:* 1 kg of API
- *Level 2. Cradle to gate and Level 3. Cradle to grave - pharmaceutical product:*
  1 defined daily dose (DDD) according to WHO definition: "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults."[42]

[41] Siegert, M-W., Lehmann, A., Emara, Y. and Finkbeiner, M. (2018) Harmonized rules for future LCAs on pharamaceutical products and processes. Int. J. Life Cycle Assessment, November 2018, pp 1-16
[42] WHO Collaboration Centre for Drug Statistics Methodology, DDD - Definition and general considerations. https://www.whocc.no/ddd/definition_and_general_considera/

Using DDD as functional unit for a pharmaceutical product is a way to reflect the function of the product, which is needed to achieve comparability of different products with the same API. The German SERUM project has taken this a step further and proposes an effect-based functional unit for pharmaceutical products, which incorporates several aspects of treatment in terms of geographical region, treated disease, period of application as well as if it is used for adult or children. An effect-based functional unit is more theoretically correct than DDD, but it will also have implications on the number of results that will need to be reported for a specific product. Specific results will need to be developed for each specific treatment scenario. Therefore, DDD may be a good starting point.

Another aspect to keep in mind in further development of the PCR and grouping of products is the principle of materiality, i.e. that reporting should focus on significant impacts. A central materiality aspect in this case is where in the life cycle the main impact occurs for specific product groups. Depending on product, significant impacts may occur in different parts of the life cycle e.g. for one type of product the main impact occurs in production of key raw material, for others the main impact may occur in the API production or formulation, whereas for a third type of product the main impact may occur in the use of the product. This should also guide further development. Perhaps products can be grouped based on where in the life cycle the significant impacts occur, and the reporting may then specifically focus on those parts of the life cycle. This could be a way to simplify data collection and reporting.

Such grouping based on impact in the life cycle, however, must be based on a sufficiently large sample of studies, to secure representativeness. As there are still few publicly available studies for pharmaceutical products, this will only be possible if internal studies that are made by pharmaceutical companies can be shared in some way, taking into account proprietary and confidentiality aspects. It should also be noted that reporting only a part of the life cycle would be a significant deviation from ISO 14025, which basically requires that all relevant parts of the life cycle shall be included. However, to make progress and get started with reporting of relevant and significant impacts, this could be a way to move forward.

Demonstration for how a PCR for pharmaceutical products may look like

A rough "embryo" for a PCR for a pharmaceutical product have been developed in the project, to show an outline and potential content of a PCR for a pharmaceutical product, see Appendix II. The content in terms of requirements is based on:

- The NHS guideline for product carbon footprint assessment[43], see also chapter 5.1.4.
- The PCR Basic Module for Other Chemical Products (UN CPC code 35) from International EPD ® System[44].
- General guidelines for structuring development of Product Category Rules (PCRs) according to ISO/TS 14027[45].

For simplicity, we have chosen to focus the document on only one process route for each of the two main stages in manufacturing of pharmaceutical products, as defined in the NHS guideline. The following routes have been selected:

[43] Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices, November 2012, https://www.sduhealth.org.uk/areas-of-focus/carbon-hotspots/pharmaceuticals.aspx
[44] EPD International (2018) PCR Basic Module Other Chemical Products; Man-Made Fibres, Product category classification: UN CPC 35, Version 3.01, dated 2018-11-06. https://www.environdec.com/PCR/Detail/?Pcr=7066
[45] ISO/TS 14027:2017 Environmental labels and declarations – Development of product category rules. ISO, Geneva. 2017

- Active pharmaceutical ingredient (API) manufacture: *synthetic organic chemical batch-processes* that start from commercially available commodity and speciality chemicals.
- Delivery mechanisms: *solid dose forms* such as tablets or a dry powder for use in a further delivery mechanism.

The other routes described in the NHS guideline are therefore not included.

The "embryo" is intended both as a demonstration for how a PCR for pharmaceutical product might look like, as well as provide input to detailed discussions in the business, to agree on requirements for how to collect, compile and report product carbon footprints for pharmaceutical products. It is NOT a final agreed PCR for a pharmaceutical product.
Note: Some elements in PCRs have been excluded in the "embryo", such as requirements for communication in terms of content and format.

5.3 Opportunities and challenges in developing product carbon footprint reporting

When data requirements and calculation rules has been agreed in the PCR, it can be used as basis to develop product carbon footprint reporting for products within the product category. An overview of the steps involved in developing product carbon footprint reporting, based on a PCR, is illustrated in Figure 7.

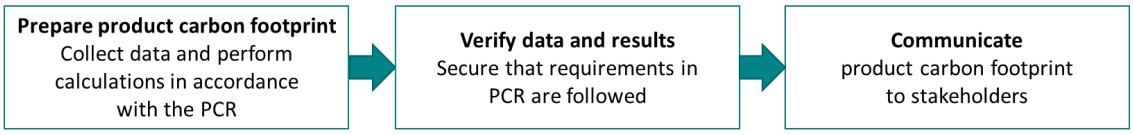

Figure 7. Steps in developing product carbon footprint reporting based on a PCR

The work involves:

- *Preparation of the product carbon footprint* in accordance with the agreed requirements in the PCR. This includes collecting data and performing calculations as prescribed by the PCR, as well as preparing the communication of the result.
- *Verification of data, calculations and results*, to secure that the agreed requirements in the PCR have been followed. The verification should be made by an independent third party, to provide external assurance of the results.
- *Communication* of the verified product carbon footprint to stakeholders as agreed in the PCR.

The proposal to initiate PCR development as basis for carbon footprint of pharmaceutical products has been discussed with the pharmaceutical companies that have participated in the project. Most agree that the EPD framework defined in ISO 14025 is a good starting point. There is, however, a number of challenges both in developing a PCR for pharmaceutical products and for the companies to compile and report carbon footprint in accordance with the PCR. Some of these are outlined and discussed below.

A general comment from the discussions is that the approach needs to be *streamlined* to allow reporting of several products at a reasonable effort, but at the same time it also needs to be on a *sufficiently detailed* level that makes it possible to distinguish differences in performance between different companies delivering the products with the same API. This is a balance which is not easy to achieve.

Another general comment from the discussion is how available information and already performed studies may be used in this context. This will need to be agreed. In principle, existing studies may be handled in the same way as new studies based on the PCR, where compliance with the agreed requirements in the PCR is verified by a third-party. Any non-conformances from the requirements in the PCR that have been found in the verification will then need to be handled.

Develop PCR – harmonization and agreement

As outlined above, in the PCR development a number of methodological principles and choices for how to compile and calculate results needs to be discussed and agreed within the business. As in any standardization effort it is not always easy to reach consensus and common agreement in discussions between different stakeholders. Key questions to agree on are e.g. definition of product category and level of detail for the PCR(s), how to handle allocation in a fair manner when several products are produced at the same production site, requirements on data collection and data compilation, etc. Practical feasibility and availability of data should also be considered.

Within the EPD framework there are a lot of experiences from development of PCRs for a wide range of products and different industrial sectors, which can be utilized to make progress in the pharmaceutical business. Also, the development in the German SERUM project[46] should be utilized, and combined with the set-up proposed in this project, to achieve a broader base and international acceptance for the requirements.

Earlier harmonization efforts in the pharmaceutical business clearly show that there is a great interest and will to contribute to the development in a constructive way, and thus there is a great potential to agree and make progress in this area.

Prepare product carbon footprint – collect data and perform calculations

Data collection is generally the most resource demanding part when developing product carbon footprints. Based on the modularized approach, with the three levels of reporting as described in chapter 5.2.2, data will be needed from three main sources:

- within the company e.g. environmental data for production, product specifications and use scenarios
- from the supply chain, e.g. suppliers of raw materials and packaging materials
- generic data in international databases and other sources

Regarding company specific data, production data is usually collected for production sites as a whole and are often not divided into the specific products produced at site. Thus, allocation of data will be needed between the products. Product specifications and use scenarios may not be defined in internal information systems as needed for this purpose. Thus, to be able to produce product specific data, usually additional data processing will be needed to adapt the data from its original

[46] Siegert, M-W., Lehmann, A., Emara, Y. and Finkbeiner, M. (2018) Harmonized rules for future LCAs on pharamaceutical products and processes. Int. J. Life Cycle Assessment, November 2018, pp 1-16

source into input data for a product carbon footprint calculation. Specific procedures may need to be established for this purpose, integrated with other data collection efforts within the company. To support this, guidelines may need to be developed for how to efficiently organize and manage product specific data collection.

Regarding supply chain, often the supply chain of a pharmaceutical product is long and complex, where the first-tier supplier (i.e. the company that provides parts and materials directly to a manufacturer) may only represent a small part of the chain. Thus, it can be difficult to collect relevant data for different parts of the supply chain. Data collection from suppliers may be difficult due to confidentiality issues, as the data needed for environmental assessment is often company internal and may be sensitive to share, as it concerns e.g. data for specific energy consumption, yields and waste generated when producing the products. Also, if a supplier does share data it can be difficult to verify and assure the quality of the data, as it is may be difficult to know how the data have been collected and compiled. Here we would recommend utilizing available industry initiatives as starting point if possible, such as the Pharmaceutical Supply Chain Initiative (PSCI)[47]. Perhaps PSCI may be further developed to include sharing of environmental performance data, to both support supplier environmental evaluation as well as be used as input in product carbon footprint reporting. As part of this e.g. shared procedures and templates for supplier environmental data collection may be developed to support the work.

Regarding generic data in international databases or other sources, it can be difficult to assess the representativeness of the data for the specific application. Also, data may be missing for specific raw materials used in pharmaceutical products. Common and shared databases for the pharmaceutical business may need to be developed, both to secure that the same generic data is used as basis for reporting within the business as well as to acquire industry common data for pharma-specific raw materials which is missing.

In addition to different supporting tools and guides for data collection, also calculation tools may need to be developed and maintained. Today, these types of calculations are often performed in dedicated specialist LCA software. Simpler tools may be needed, in order to establish a broader base for reporting by different companies. Experiences and parts from the ASC and ABPI footprint tools (see chapter 5.1.4) could be used as starting point for such simpler tools.

Within the EPD framework there are also a number of initiatives aimed at developing how data collection and reporting can be streamlined, to enable and facilitate cost-efficient reporting for a full product portfolio. For example, there are pre-verified EPD tools that contain data and calculation models to simplify the LCA calculation based on a reference PCR[48]. Such tools are pre-verified to ensure that it produces correct data, given the correct input, which simplifies the development of the EPD. We recommend keeping updated on the progress in these initiatives, and evaluate if tools and methods may be used and/or adapted for the pharmaceutical business.

Verify data and results

According to ISO 14025, an independent third-party verification of data and results is required, to provide external assurance that data and results have been collected and calculated in accordance

[47] PSCI Pharmaceutical Supply Chain Initiative. https://pscinitiative.org/home
[48] Pre-verified EPD tools, EPD International. https://www.environdec.com/Creating-EPDs/Steps-to-create-an-EPD/Perform-LCA-study/pre-verified-epd-tools/

with the agreed requirements in the PCR. Also, the communication of results should be verified to secure that requirements for communication is followed.

Specific requirements for verification will depend on which option which is chosen for PCR development (see chapter 5.2.1). If an existing EPD program is selected, then the procedure for verification is defined by the program. If, however, the pharmaceutical business chooses to start an independent program or only utilize parts of ISO 14025, then specific requirements on verification needs to be developed and agreed within the business. In the latter case, we still recommend to utilize the experiences for how verification is made in established EPD programs.

A key aspect in the verification process will be how to secure and maintain confidentiality and other proprietary issues.

Communicate results

Principles and requirements for communication of results is defined as one part of the PCR, in terms of e.g. content and format of communication. Thus, this will need to be defined and agreed within the pharmaceutical business.

In the development, the actual intended use and applications of the information must be clarified and understood, in order to develop communication that is relevant and facilitates interpretation and use of the information for different stakeholders. For example, different ways of communication are possible:

- as quantitative results, which is the case in most EPD programs. This will allow for detailed comparisons of products as well as allows for calculations of environmental impacts of pharmaceutical use e.g. for a specific treatment scenario or for follow-up impacts of total annual use
- in relation to a benchmark where the benchmark can represent as an average product in the product category, which has been tested within EUs initiative Product Environmental Footprint (PEF). This will facilitate quick assessment for a specific product and could e.g. be used in consumer communication.

Thus, different means of communication may be needed, depending on the intended use and applications.

6 Potential use of the information by different stakeholders

The main focus in this project has been on developing and proposing a common assessment model for product specific and comparable environmental information for APIs and pharmaceutical products, in terms of environmental risk and carbon footprint. In addition, opportunities and challenges for pharmaceutical companies to compile and report information based on the model has been explored.

Reporting and communication of environmental information should, however, be adapted to its intended application and use. This chapter outlines potential use of the information for different purposes by different stakeholders. As a general principle, environmental information should be used as basis to control, manage and reduce impacts along the pharmaceutical value chain, and drive improvements in different parts of the chain. Different actors along the chain will have different roles and responsibilities in this, and can use the information in different ways, as indicated in Figure 8.

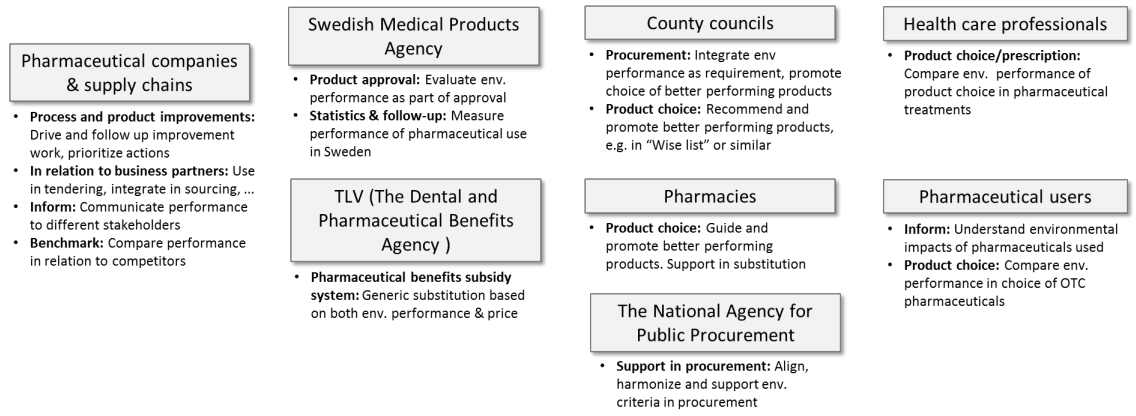

Figure 8. Examples of potential use of product specific environmental information by different stakeholders along the Swedish pharmaceutical value chain

Based on this, we have identified the following key potential applications and use for the information:

- Assessments in conjunction with product approval
- Pharmaceutical benefits subsidy systems
- Procurement
- Process and product improvements
- Guidance in product choice

These applications are described in the following subsections.

It should be noted that it is a challenge to find an environmental assessment model that delivers results which is adapted to all purposes and any potential applications. This chapter indicates potential uses of the proposed model, but no detailed assessments have been made of the actual suitability to meet specific use requirements. Further studies will be needed to assess this, and the results from such assessments should be used as basis to guide further development of the

proposed model. As part of this, it is also important to identify and assess training and competence requirements for the users of the information, to secure that the information can be correctly interpreted and used.

Nevertheless, securing alignment and harmonization of environmental information requirements between different applications and stakeholders is strongly recommended for several reasons, and should be utilized as far as possible, as this will increase both quality and availability of information. For the companies and organizations that are expected to deliver the information, it is time-consuming and costly to acquire and compile information according to different methods and in different formats. Also, errors may be introduced when transferring and processing data and information from its original form. This should be considered by the stakeholders requesting information. When requesting information, requirements and use of the information should be clearly specified, including the incentives for sharing and delivering the information. For example, in procurement tenders the weight that the information has in the procurement decision should be clearly specified, to enable equal and fair comparison and competition.

6.1 Product approval

When a new pharmaceutical product is about to be introduced on the market, it must go through an approval process through market authorization, unless the new product differs only slightly from a previously approved product. Product approval for marketing authorization within the EU has to be processed either through the European Medicines Agency (EMA) or national agencies depending on type of the authorization process - centralized approval or national approval. Centralized product approval is used if the producing company wishes the product to be approved in more than one-member state[49]. After such an approval, the product can be sold on the entire EU market.

The centralized product approval is administrated by EMA, while the scientific investigation is carried out by medical products agencies in a reporting and a co-reporting country, each of which conducts an independent evaluation. The results are shared with other member states and the final decision is made by the European Commission based on the opinion from a special scientific committee. If the benefits of the medicine are greater than its risks, the product can be approved. There is also a possibility of mutual recognition, where approval is initially sought in a member state (reference country), which carries out the scientific evaluation. The evaluation and authorization then form the basis for application in other member states, which thus do not need to repeat the evaluation but instead 'mutually' accept the investigation of the reference country. National product approval in Sweden is administered and carried out by the Swedish Medical Products Agency.

The authorization procedures include an environmental risk assessment (ERA), but the main prerequisite for a product to be approved is that it has been found appropriate as a medicine based on risks vs. benefits focusing on a medical/clinical human health perspective. Local ERA and product carbon footprint information, as proposed in this project, could supplement the existing environmental information in the approval phase, and provide a broader understanding of the environmental consequences of the product. But in accordance with current practice and in line

[49] https://lakemedelsverket.se/english/overview/About-MPA/Activities/Medicines/Approval-of-new-medicines/

with the EU Strategic Approach to Pharmaceuticals in the Environment[50], the focus for approval should remain on risks vs. benefit from a health perspective.

6.2 Pharmaceutical benefits subsidy systems

There has been a gradual increase of the societal costs for purchasing pharmaceuticals during recent years. The purchase value has almost doubled since the beginning of this century. In 2015, the total sales of pharmaceuticals for human use amounted to roughly SEK 40 billion, of which SEK 28 billion were sales of prescribed pharmaceuticals, SEK 8 billion were for purchases for hospitals and SEK 4 billion were selfcare pharmaceuticals[51].

A major part of prescribed pharmaceuticals falls under the *Law on Pharmaceutical Benefits Subsidy System*[52], where pharmacies are obliged to replace prescribed pharmaceutical with the cheapest available equivalent one, also referred to as "generic substitution". Pharmaceutical subsidy systems exist also in some other countries, e.g. in Australia, Malaysia, New Zeeland and the UK. In Sweden, the Dental and Pharmaceutical Benefits Agency, TLV, is the central government agency whose remit is to determine whether a pharmaceutical product, medical device or dental care procedure are replaceable and could be subsidized by the state[53]. Those pharmaceuticals that are replaceable are regularly listed on a monthly basis (*product of the month*). Only products included in the *Law on Pharmaceutical Benefits Subsidy System* can be subject for being replaced.

Today the pharmaceutical benefits subsidy system is purely based on cost, where lowest offered price seems to be the main criteria in selection of suppliers and products.

As the subsidy system involves substantial volumes of pharmaceuticals, it is specifically important to include environmental aspects as one of the selection criteria in the system, since this has a great potential to drive improvements and reduce of environmental impacts of the use of pharmaceuticals in Sweden. This has been discussed for many years, but there is still no progress on the subject. Several interested parties have specifically mentioned the lack of product specific environmental information and criteria as the main explanation for this. The model proposed in this project could be used as input to make some further progress in this.

Adding environmental aspects as one selection criteria could shift the current consistent focus on lowest offered price, to a broader evaluation taking into account environmental impacts. This may, however, imply additional costs for the system, and therefore there is also a need for clear political directives and requirements. It should be noted that the aim of TLV´s pharmaceutical subsidy system is to "acquire as much health as possible for the tax-payers money going to medicines"[54] and that human health aspects are subordinate environmental properties when prescribing pharmaceuticals. Thus, the mandate of TLV may need to be updated to allow for further environmental considerations.

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[50] European Union Strategic Approach to Pharmaceuticals in the Environment. http://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF
[51] eHälsomyndigheten, Detaljhandel med läkemedel 2015. https://www.ehalsomyndigheten.se/globalassets/dokument/statistik/detaljhandel_med_lakemedel_2015_1.pdf
[52] Lag (2002:160) om läkemedelsförmåner m.m. http://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-2002160-om-lakemedelsformaner-mm_sfs-2002-160
[53] TLV The Dental and Pharmaceutical Benefits Agency. https://www.tlv.se
[54] TLV The Dental and Pharmaceutical Benefits Agency. https://www.tlv.se

6.3 Procurement

The procurement of pharmaceuticals by Swedish country councils is regulated by legislation and directives for public procurement. Of the total spend for pharmaceuticals in Sweden, the share under public procurement is approximately 20 per cent[55].

In 2014, EU launched a new updated Directive on Public Procurement followed by several initiatives in the Members States to establish national Public Procurement strategies and legislation. Probably the most important new feature in the EU Public Procurement Directive is that the evaluation and assignment of a winning bid can be based on the use of award criteria focusing on "the best economic advantageous tender" (also referred to as *Best value for money*). This approach adds other components to the principle of "lowest price", which can include environmental considerations. This means that Green Public Procurement (GPP) may play a more significant role in public procurement, compared what was the case before. In the EU about half of public contracts are based on the principle of lowest price, and a recommendation to the Member States has been forwarded to try to include other aspects in the award phase, where environmental concerns should be prioritized.

According to EU:s definition, Green Public Procurement (GPP) means that public authorities seek to purchase goods, services and works with a reduced environmental impact throughout their life-cycle compared to goods, services and works with the same primary function which would otherwise be procured[56]. In this way, Green Public Procurement is a potentially powerful tool to both gain environmental and economic benefits and to minimize risks and drive research activities toward new innovative and environmentally sound technologies and processes. The work on the new EU Directive on Public Procurement was followed by identifying new product categories to be subject for Green Public Procurement (GPP) and included in the "EU GPP Tool"[57]. Pharmaceutical products are not yet in this list but might become a candidate, resulting in a more widely use of GPP for pharmaceuticals in Europe in the future.

A recently finished study carried out as a sub-project funded by Interreg and led by the Stockholm International Water institute (SIWI) on GPP of pharmaceuticals in the Baltic Sea Region (GrePPP) describes the current status in a number of countries in the region regarding GPP, with the overall ambition to find support and a mechanism to establish and launch an international platform on the subject. The study shows that, for the time being, GPP seems to be a subject with little attention and practical work[58]. Despite of this there was generally a great awareness and concern about the environmental risks with production and use of pharmaceuticals, and the potential of minimizing these risks by making better use of public procurement.

Some separate initiatives have, however, recently been taken in the Nordic countries. In Sweden, the National Agency for Public Procurement has published an updated proposal for procurement criteria for pharmaceuticals including API-production and product environmental information

[55] Lonaeus, K. (2016) Hållbara läkemedel – Upphandling som styrmedel. SIWI, Report 2016, ISBN: 978-91-981860-9-3
[56] European Commission, What is GPP. http://ec.europa.eu/environment/gpp/what_en.htm
[57] European Commission, GPP Training Toolkit. http://ec.europa.eu/environment/gpp/toolkit_en.htm
[58] Ryding, S-O., Alhola. K., Aliojo, A., Jegelevicius, G., Lauri, Ä., Moch, K. & Pagh-Skov, L. (2018) Green Public Procurement of pharmaceuticals in the Baltic Region, SIWI, Draft Report 2018-11-18

focusing on climate[59]. A public consultation of the proposal has recently been performed. The Norwegian purchasing organization Sykehusinnkjop has developed environmental criteria based on environmental risk management, including procedure for follow-up through desk and on-site audits (see also chapter 4.1). In Finland, some hospital pharmacies organize tender competitions of pharmaceuticals used by public health care and undertake joint procurement and related co-operations. In Sweden, the County Councils are regularly using social and environmental criteria in its procurement of pharmaceuticals, and follow-up compliance by collecting information from the suppliers. The social criteria used in procurement in all 21 County Councils are based on the politically adopted Code of Conduct for Suppliers[60]. The environmental criteria that are used may, however, differ between different County Councils as they are often defined based on regional environmental goals.

The model for comparable and verified local ERA and product carbon footprint proposed in this project could be used as basis in further development of environmental criteria for public procurement and may in this way strengthen the different initiatives around GPP. This should also include needs for competence development and training of the different functions involved in procurement, to secure that results from the model can be correctly interpreted and used.

6.4 Product and process improvements

Product specific environmental information, based on the model proposed in this project, can be used in a number of different ways to drive product and process improvement work, such as:

- identify improvements opportunities in different parts of the life cycle (e.g. in supply chain, own operations or in use phase) as well as within the product portfolio (e.g. products within the portfolio which has a high environmental impact)
- prioritize and plan improvement actions and define targets and KPIs, both internally and in collaboration with business partners along the chain
- follow-up results from implemented improvements

Results from the carbon footprint assessment can for example be used to identify “hot spots” in terms of raw materials and process steps which has a large contribution to the overall footprint. Based on this, improvement opportunities can be identified and prioritized, such as substitution of chemicals with a lower footprint, process efficiency improvements, adapting administration and guidance for use to minimize impacts in use phase, etc.

The results from the local environmental risk assessment can be used to compare risks between different sites producing the same API, and to identify risks in supply chain in terms of localization. This can e.g. be used in strategic planning of sourcing and decisions in localization of production sites.

Several pharmaceutical companies are already using this type of information to guide product development, product and process improvements and strategic planning. There is, however, a potential for broader use within the industry and for use in new applications. For example, in stimulating and incentivizing collaboration between different stakeholders to follow-up and

[59] Upphandlingsmyndigheten, February 2019. https://www.upphandlingsmyndigheten.se/aktuellt/tyck-till-om-hallbarhetskriterier-for-lakemedel/
[60] Hållbar upphandling- Ett samarbete mellan Sveriges landsting och regioner. www.hållbarupphandling.se

reduce impacts along the life cycle, upstream in the supply chain with suppliers and sub-suppliers, and downstream in the use and end of life phase.

In addition, the results could be used for benchmarking performance in relation to competitors, if different companies are reporting and publicly sharing the information.

6.5 Guidance in product choice

Comparable and verified product environmental information can also be used to guide product choice, by county councils, healthcare professionals and pharmacies, to take active decisions and choose products that have a lower environmental impact. It may also ultimately be used by consumers who want to stay informed of environmental impacts of the products they use.

County councils and healthcare professionals

Several county councils have a pharmaceutical committee that prepares guidelines and recommendations for product choice, which are used by healthcare professionals in prescription of pharmaceuticals. One such example is the "wise list" prepared by Stockholm county council, where recommendations are based on scientific documentation regarding effect and safety, pharmaceutical efficiency, cost effectiveness and environmental aspects[61]. Today, the environmental part of the assessment is largely made based on the current available environmental classification at Fass.se and is thus fairly limited. The environmental information resulting from the proposed model would greatly improve the possibility to make a sound environmental assessment as basis for these recommendations. If recommendations favor pharmaceuticals with a lower environmental footprint when it is possible, they have a potential to reduce the county council´s overall environmental impacts of pharmaceutical use.

The information may also be used directly by healthcare professionals themselves, to make their own environmental evaluation for product choices in therapeutic treatments, when there are different options of products with equivalent medical effects. To facilitate this, the information needs to be easily available and accessible, such as on Fass.se. It should be noted that this may also require additional training of the healthcare professionals on how to interpret and use the information, to secure that the information can be used correctly.

Pharmacies

The pharmacies have a potential in supporting and guiding pharmaceutical users in terms of environmental aspects and performance. But to be able to do so, relevant and reliable information is needed. This is highlighted among the Swedish Pharmacy Association´s requirements on pharmaceuticals, where one of their key requirements is that they want to be able to answer questions regarding environmental impacts of pharmaceutical products[62]. This information is not available today, except for the existing environmental classification information available at Fass.se.

[61] Janusinfo Region Stockholm, Kloka listan. http://klokalistan2.janusinfo.se/20191/
[62] Sveriges Apoteksförening, Läkemedel och miljö. http://www.sverigesapoteksforening.se/miljo/

Some pharmacies have developed their own environmental criteria, evaluations and labels to guide product choice towards more environmentally sound alternatives. One such example is the pharmacy chain Apoteket Hjärtat and their sustainability label "Choose by the heart" for over the counter (OTC) pharmaceuticals[63]. The label is based on their own set of criteria which is based on a supplier evaluation, rather than a product specific evaluation. The pharmaceutical suppliers have the possibility to label their products when they fulfil all of the following requirements: a third party verified sustainability report equivalent to the GRI (Global Reporting Initiative) standard, a membership in PSCI (Pharmaceutical Supply Chain Initiative), and the products does not include specific pollutants according to Swedish legislation for water quality. A harmonized and comparable way of reporting product specific environmental information could enable harmonized and well defined "green" labels for pharmaceutical products.

7 Conclusions and recommendations for next steps

The focus of this project has been to develop and propose a model for how local environmental risks of API emissions from manufacturing and carbon footprint in a life cycle perspective may be acquired, verified and reported for pharmaceutical products, to enable comparison of products with the same API.

The results from the project show that the local environmental risk part may be implemented within the existing framework for environmental classification at Fass.se. It has been assessed to be possible for pharmaceutical companies to perform in its current form, and it may be included in the FASS guideline, to enable companies to report in accordance with the model. Before implementation, however, some further development is needed, which includes pilot tests to secure that data collection and reporting can be done in an equivalent manner by different companies, additional development of review and verification procedures for the reported information, as well as development of how the local ERA results can be communicated at Fass.se.

The product carbon footprint part, on the other hand, requires additional harmonization and development within the pharmaceutical business to find a practical and feasible set-up that will enable a broad base for reporting by different pharmaceutical companies, that can secure comparability between products and suppliers. The ISO 14025 framework for Environmental Product Declarations is proposed as basis, where the first step is to initiate development of Product Category Rules (PCR) for pharmaceutical products. There are a number of different options for how to proceed with this, which needs to be agreed within the industry. It is also strongly recommended to perform PCR development as an international effort, to secure that the same requirements can be used in different markets. The industry is, however, in a good position to make progress in this area. There is a wealth of experiences and work that can be utilized a basis, both within the pharmaceutical industry as well as in other industries. The pharmaceutical industry also has a tradition to collaborate and share experiences through the different environmental and sustainability initiatives to harmonize, develop and improve environmental and sustainability management within the business.

[63] Apotek Hjärtat, Välj med Hjärtat. https://www.apotekhjartat.se/om-oss/valj-med-hjartat/

Further implementation and development of the model should, however, be based on the actual intended use of the information by different stakeholders. Therefore, the intended use must be clarified. Product specific environmental information, as proposed in this project, has a potential to be used for a wide variety of different applications to control, manage and reduce impacts along the pharmaceutical value chain, and drive improvements in different parts of the chain (see discussion in chapter 6). Different actors along the chain will have different roles and responsibilities in this and may use the information in different ways. This needs to be better understood, as different uses of information will put different requirements on the information and the reporting.

It should be recognized that it may be difficult to find an environmental assessment model that delivers results which is adapted to all purposes and any potential applications. For example, there is a difference in requirements if the information is only to be used to improve general environmental awareness, or if it shall be used as selection and award criteria in public procurement and the generic substitution system. In the latter case, the information needs to hold for strict review procedures.

Recommendations for next steps and further development

Based on the results from the project, we propose two main areas for next steps and further development:

- Clarify the needs, requirements and use of product specific environmental information for pharmaceuticals; by different stakeholders and for different applications
- Continue harmonization, development and implementation of the proposed model in the pharmaceutical business, based on requirements and intended applications

Both areas will require collaboration, not only between pharmaceutical companies, but between all relevant stakeholders along the pharmaceutical value chain.

To *clarify needs, requirements and use of the information by different stakeholders*, we propose to perform a stakeholder analysis which should include the following activities:

- Identify and map roles and responsibilities of different stakeholders in the work to reduce environmental impacts along the pharmaceutical value chain, both in terms of current status and potential new/changed responsibilities.
- Based on the mapping:
    - Define where and how product specific environmental information can be used to prioritize, measure and follow-up improvements along the chain
    - Identify drivers, incentives and barriers for reporting and using product specific environmental information along the chain, both internal within an individual organization and in collaboration with other actors along the chain. This should also include an evaluation of policy and regulations that may support or hinder implementation, e.g. in the generic substitution system, in procurement, etc.
    - Identify knowledge and competence requirements for different stakeholder functions/processes along the chain in using product specific environmental information in a correct way, e.g. purchasers, healthcare professionals, pharmacists, …

The analysis should be conducted through multi-stakeholder workshops, combined with interviews with key stakeholders and literature review. The newly started Competence Center for

Pharmaceuticals[64] could be utilized as a platform for this, starting from the results and experiences from this project as well as other ongoing related activities, such as the Swedish National Agency for Public Procurement work with criteria for pharmaceutical products.

The results from the stakeholder analysis in terms of needs, requirements and use of information should guide *continued harmonization, development and implementation of the proposed model* for different applications.

As described in this report, further development and harmonization is needed of both parts of the model before implementation may start. In addition, synergies and communication of the combined result from the model should be defined, i.e. how to correctly interpret and use the combined result from the local ERA and carbon footprint part. It should also be decided where to start implementation based on feasibility and identified prioritized needs; e.g. for prescribed pharmaceuticals (Rx) within the generic substitution system, and/or for OTC products.

Recommendations for the local ERA part is described in chapter 4.3, and includes pilot tests, development of review and verification procedures, update of FASS guideline and web-application, as well as defining how the information should be communicated at Fass.se. Further development of the carbon footprint part is outlined in chapter 5.2.2 and 5.3, where the first step is to decide option for how the development of a PCR for pharmaceutical products should be performed, as well as how to define product categories in line with identified information needs and requirements. Based on this, modularized PCR development can be started. An important part of the PCR development is also to define and agree requirements for verification and communication of results. The development should also identify needs for guidelines, tools and databases to facilitate and support efficient data collection, compilation and calculations for the companies when developing and preparing comparable and verifiable product carbon footprint information for pharmaceutical products.

[64] Kunskapscentrum för läkemedel i miljön, Verksamhetsplan 2019-2023, Läkemedelsverket, december 2018

Glossary of terms

API	Active Pharmaceutical Ingredient
ERA	Environmental Risk Assessment
Local ERA	in this report referred to as local environmental risk assessment of emissions of API from production of API and/or from formulation and packaging of pharmaceutical products
PEC	Predicted Environmental Concentration
PEC_{local}	Predicted Environmental Concentration at the site of primary local emission of API (e.g. at manufacturing site)
PNEC	Predicted No Effect Concentration
RCR	Risk Characterization Ratio
LCA	Life Cycle Assessment
EPD	Environmental Product Declaration
PEF	Product Environmental Footprint
PCR	Product Category Rules
PEFCR	Product Environmental Footprint Category Rules
GPP	Green Public Procurement
PSCI	Pharmaceutical Supply Chain Initiative

Appendix I. Environmental risk

The two parts of the proposed model for environmental risks in manufacturing of pharmaceutical products is presented in the following subchapters.

- The questions in Part 1 relating to environmental risk management is adopted as is from the procurement organization for hospitals in Norway (Sykehusinnkjöp). Note: the questions have been translated from Norwegian and they have also been slightly adapted for this purpose.
- The model for local ERA of API emissions from production described in Part 2 is a further development of the current environmental risk model and classification at Fass.se

Part 1. Environmental risk management

1. Requirements relating to the supplier´s environmental strategy

The supplier should have an overall environmental strategy that covers the entire product portfolio. If not – what has been excluded?
Free text

The supplier should have an overall environmental strategy that covers the entire value chain from raw material to finished product. If not – what has been excluded?
Free text

2. Requirements linked to the supplier's overall environmental strategy for risk management and environmental audits

Will the supplier be willing to disclose in which/what country the API/raw material production occurs for the reported products?
YES / NO

Does the environmental strategy apply to the production facilities that produces the finished products?
YES / NO

Does the environmental strategy apply to API/raw material producer(s)?
YES / NO

Does the environmental strategy apply to waste water treatment plants (on-site or off-site) for API/raw material producer(s)?
YES / NO

Does the environmental strategy include mass balance calculations and/or monitoring of discharges and corresponding environmental risk assessments
YES / NO

3. Requirements linked to the supplier's procedures for conducting environmental audits and willingness to share results from environmental audits

The supplier should have procedures for conducting environmental audits for procurement, production and disposal of APIs / raw materials, and is requested to describe the scope of such procedures, including any frequency for performing environmental audits.
Free text

The supplier should be willing to share results from environmental audits conducted, including who made environmental audits, and be asked to describe the extent to which such results can be presented upon request.
Free text

4. Requirements related to the supplier's follow-up of procedures relating to environment. The requirements apply from the acquisition of API raw materials, production up until emissions in connection with production.

The supplier should provide an overall summary of their environmental procedures.
Free text

The supplier should describe whether the environmental procedures apply to both the supplier's factory/factories and/or the API/raw material producer(s).
Free text

The supplier should state whether third-party manufacturers are given training in the supplier's environmental procedures.
Free text

The supplier should state whether sampling of waste water from the API/raw material producer(s) is carried out, as part of the supplier's environmental risk assessment.
Free text

The supplier should state whether mass balance calculations of waste water from the API / raw material producer (s) are carried out, as part of the supplier's environmental risk assessment.
Free text

Part 2. Local environmental risk assessment of pharmaceutical emissions

- **Emission(s) of product API (A):** Calculate the amount of API which reaches the primary receiving water bodies via waste-water (kg/year) after production of the API, formulation and any other relevant sources of API emissions. Please report separate values only if the recipients are separately located, otherwise, add the amount of API emissions together. The API emissions can be calculated via theoretical yield minus produced amount. The amount of API is usually calculated by mass balance/yield analysis calculations. Based on the path of synthesis and the amount of input of raw material the theoretical yield can be calculated. By comparing that number to the amount that has been produced, it is possible to estimate the amount of substance that has been lost to the environment. If the company perform representative sampling and chemical analysis of effluents, this may also be used as basis. Only the amount of emitted API

needs to be reported, but background information and the full calculation should be reported on request.

- **Removal rate (R)**: If the waste-water is treated before entering the recipient(s) and API is removed in the process, it is possible to use a removal rate (%) in the calculation of PEC_{local}. If a removal rate is used, a justification of the reported rate should be provided. The full calculation and background information should be reported on request.

- **Waste water volume (V):** Report the waste-water volumes through which API is released to the environment, for all relevant sites (L/year). Only the volume of waste water needs to be reported, but the full calculation should be reported on request.

- **Dilution factor (D):** Describe the localization(s) of the water body that receives the (treated) waste-water from the API production, formulation of tablet and any other relevant sites of API emissions. The description should preferably be on region/city/name of recipient, or at least at a national level (country). Based on that information, extract the relevant dilution factor from Keller[65], see Figure 9. Companies are, however, encouraged to use their own value for dilution, but then the calculation must be reported in full.

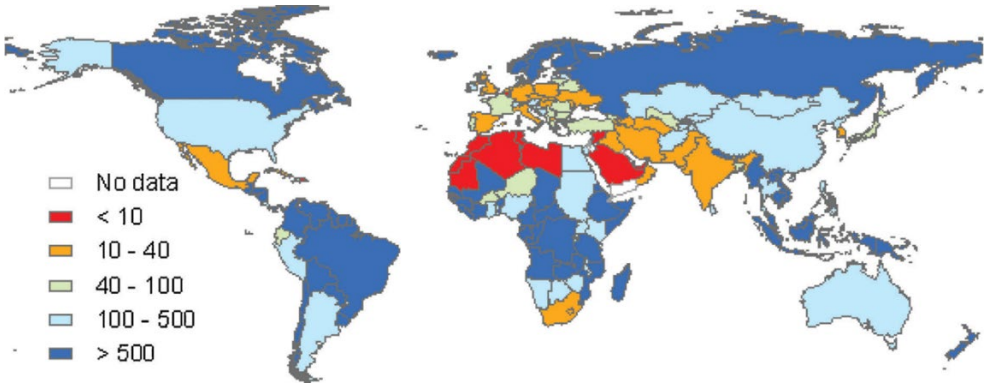

Figure 9. Modelled dilution factors per country from Keller et al (2014).

- **Local predicted concentration (PEC_{local})**: Calculate PEC_{local} (µg/L) = (**A***10^9*(100-**R**))/(**V*****D***100). The factor of 10^9 in the equation converts the quantity used from kg to µg. If several values are produced due to several sites of API emissions (and they differ), the highest value should be chosen for the following steps.

- **Predicted no effect concentration (PNEC)**: Calculate a PNEC (µg/L) of the API on three trophic levels in the aquatic environment based on own or acquired data using the method described in the FASS guideline[66]. If no PNEC data is available for the API, it is not possible to calculate the risk characterization ratio (RCR) and thus a full environmental risk assessment cannot be performed.

[65] Keller, V.D.J., et al. (2014) Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors. Environmental Toxicology and chemistry. Vol 33, no 2 447-452. https://setac.onlinelibrary.wiley.com/doi/epdf/10.1002/etc.2441

[66] FASS guideline - Environmental classification of pharmaceuticals at www.fass.se. (2012) Guidance for pharmaceutical companies. http://www.fass.se/pdf/Environmental_classification_of_pharmaceuticals-120816.pdf

- **Risk characterization ratio (RCR) and risk phrase**: Calculate the RCR: PEC_{local} (µg/L)/PNEC (µg/L), and choose the corresponding risk phrase:

    - PEC_{local} /PNEC-ratio is <0.1
      the product API constitute an "insignificant environmental risk".
    - PEC_{local} /PNEC-ratio is >0.1 and ≤1
      the product API constitute a "low environmental risk".
    - PEC_{local} /PNEC-ratio is >1 and ≤10
      the product API constitute a "medium environmental risk"
    - PEC_{local} /PNEC-ratio is >10
      the product API constitute a "high environmental risk"

Example: Local environmental risk assessment of pharmaceutical emissions

This is an example of how the model works, using fictitious data, and could be used as a basis for a guideline.

- **Emission(s) of API (A) [kg] (**total emission of API to waste-water per year**):**
  A = 10 kg/year, only one site.

- **Removal rate (R)** [%] (due to removal in waste water treatment facilities, = 0 if no data is available):
  R = 5 %.

- **Waste water volume (V) [L]** (volume of waste water discharged per year**):**
  $V = 400 \times 10^6$ L per year.

- **Dilution factor (D)** (factor for dilution of waste water by predicted annual median dilution factors (Ref. I))**:**
  The site is located in country C, where the dilution factor is D=36.

- **Local predicted environmental concentration (PEC_{local})** is calculated according to the following formula: PEC_{local} [µg/L] = $(A*10^9*(100-R))/(V*D*100)$

  Based on data given above, this results in:
  ***PEC_{local}** = $(10*10^9*(100-25)) / (400\ 000\ 000*36*100) = 0.5$ µg/L*

- **Predicted no effect concentration (PNEC)**:
  It is assumed that the ecotoxicity data for the API and a PNEC is calculated and available at Fass.se.

  Effect level for most sensitive species from the ecotoxicological studies

  Algae (Latin name):

  - EC50 xx h (endpoint) = xx µg/L (guideline) (Reference)
  - NOEC = xx µg/L (guideline) (Reference)

Example:
Green Algae (Pseudokirchneriella subcapitata)

- *EC_{50} 72 h (growth rate) = 230 µg/L (OECD 201) (ref x)*
- *NOEC 72 h (growth rate) <100 µg/L (OECD 201) (ref x)*

Crustacean (Latin name):

- Acute toxicity: EC_{50} xx h (endpoint) = xx µg/L (guideline) (Reference)
- Chronic toxicity: NOEC xx days (endpoint) = xx µg/L (guideline) (Reference)

Example:
Giant Water Flea (Daphnia magna)

- *EC_{50} 48 h (immobility) = 50 µg/L (OECD 202) (ref x)*
- *NOEC 28 days (reproduction) = 15 µg/L (OECD 211) (ref y)*

Fish (Latin name):

- Acute toxicity: LC50 xx h (endpoint) = xx µg/L (guideline) (Reference)
- Chronic toxicity: NOEC xx days (endpoint) = xx µg/L (guideline) (Reference)

Example:
Zebra Fish (Danio rerio)

- *LC_{50} 96 h (mortality) = 1700 µg/L (OECD 203) (ref x)*
- *NOEC 14 days (hatching rate) = 360 µg/L (OECD 210) (ref y)*

PNEC [µg/L] = lowest NOEC [µg/L]/AF
Where AF= assessment factor.

Example:
NOEC for Daphnia magna (=15 µg/L) has been used for this calculation since it is the most sensitive of the three tested species.
Three tested species with chronic tests justifies an AF of 10.

*This gives **PNEC** = 15 µg/L/10 = 1.5 µg/L*

- **Risk characterization ratio (RCR) and risk phrase**:

PEC_{local}/PNEC = xx/xx = xx, i.e. PEC/PNEC <0.1/ >0.1 and ≤1/>1 and ≤10/>10 which justifies the phrase 'Emissions from production of *name of the product* has been considered to result in insignificant/low/moderate/high environmental risk.'

Example:
Based on results above; PEC_{local} = 0.5 µg/L and PNEC = 1.5 µg/L gives:
PEC_{local}/PNEC = 0.5 / 1.5 = 0.3

The PEC_{local} / PNEC-ratio is >0.1 and <1 which means that:
The Substance x has been considered to result in a "low environmental risk"

Appendix II. PCR ”embryo”

Introduction

As described in chapter 5.2 we propose to utilise the established framework for Environmental Product Declarations, according to ISO 14025, as starting point for product carbon footprint reporting. This proposal was discussed at a workshop on October 22, 2018 with representatives from pharmaceutical companies. Based on the discussions it was decided to develop an “embryo” for Product Category Rules (PCR) for pharmaceutical products.

The PCR “embryo” is intended both as a demonstration for how a PCR for pharmaceutical product might look like, as well as input to more detailed discussions to agree on requirements for how to collect, compile and report product carbon footprints for pharmaceutical products. It is NOT a final and agreed PCR. Note: In this PCR “embryo” some elements in PCRs have been excluded, such as requirements for communication in terms of content and format.

Based on the definition of product category, the PCR “embryo” describes draft rules, requirements and guidelines for developing an EPD for the product category in accordance with the main phases of an LCA (Goal and scope, Life cycle inventory and Life Cycle Impact assessment).

The content in terms of requirements is based on:

- the “Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices”, in the document referred to as *“NHS guideline”*[67].
- the PCR Basic Module for Other Chemical Products (UN CPC code 35) from EPD International, in this document referred to as *“PCR basic module”*[68].
- general guidelines for structuring development of Product Category Rules (PCRs) according to ISO/TS 14027[69].

In the document it is indicated which of the source documents that have been used as basis. Regarding the NHS guideline it is also indicated if some adaptations have been made from the NHS guideline or if the text is copied as is, directly from the guideline.

For simplicity, the document focuses on only one process route described in the NHS guideline, for each of the two main stages. The following routes have been selected:

- Active pharmaceutical ingredient (API) manufacture: *synthetic organic chemical batch-processes* that start from commercially available commodity and speciality chemicals;
- Delivery mechanisms: *solid dose forms* such as tablets or a dry powder for use in a further delivery mechanism;

Other routes described in the NHS guideline are not described.

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[67] Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices, November 2012, https://www.sduhealth.org.uk/areas-of-focus/carbon-hotspots/pharmaceuticals.aspx
[68] EPD International (2018) PCR Basic Module Other Chemical Products; Man-Made Fibres, Product category classification: UN CPC 35, Version 3.01, dated 2018-11-06. https://www.environdec.com/PCR/Detail/?Pcr=7066
[69] ISO/TS 14027:2017 Environmental labels and declarations – Development of product category rules. ISO, Geneva, 2017

PCR "embryo" content

Scope of PCR

Product category definition and description

The product category defines the categories of products covered by the PCR. The product category shall, as far as possible, relate to the function of the product, i.e. that the same functional unit may be applied to products within its scope.

The production of pharmaceutical products can be broadly split into two major stages:

- API manufacture
- Formulation with a suitable delivery mechanism for administration to patients.

This document includes:

- Active pharmaceutical ingredient (API) manufacture produced by **synthetic organic chemical** batch-processes that start from commercially available commodity and speciality chemicals;
- Delivery mechanisms in **solid dose forms** such as tablets or a dry powder for use in a further delivery mechanism;

Synthetic organic chemical: Organic synthesis covers the construction of organic compounds through reactions involving solvents. Chemical feedstocks from various sources typically undergo transformations and are then purified to make APIs. A survey indicating the types of chemical transformations which are used in the synthetic manufacture of APIs has been published and includes alkylation, acylation, deprotection and functional group interconversion.

Examples of APIs manufactured through organic synthesis may include:

- Acetaminophen (eg paracetamol);
- Aspirin (eg acetylsalicylic acid);
- Sildenafil citrate;
- Various nutritional supplements.

Solid dose forms (eg tablets and powders) are one method of delivering the API. The API is habitually mixed with excipients (eg fillers and binders) to produce the powder. Tablets are then moulded and coated for use. Powder can also be used in other forms (eg capsule, inhalers, etc), and may thus be combined with other delivery mechanisms.

The text above is based on NHS guideline. For simplicity only one route of API and Delivery mechanism has been included in the following texts.

Geographical region

The PCR is applicable to be used globally

Functional unit/Declared unit

The functional unit is the base unit for which the results are reported.

For a **finished API (Active Pharmaceutical Ingredient)** the functional unit is:

- For APIs manufactured in solid form, the output reference flow should be reported on a mass basis, ie per kilogramme of API.
- For APIs delivered in liquid form, the reference flow should still be provided on a mass of API basis however the concentration of the API should also be reported.

For a **finished pharmaceutical product,** the functional unit is:

- One Defined Daily Dose (DDD) according World Health Organization (WHO) definition. All data for finished pharmaceutical products should be reported per functional unit. ” The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. (https://www.whocc.no/ddd/definition_and_general_considera/)”
- For pharmaceuticals where DDD have not been assigned, an equivalent measure as the DDD should be used.

Note: for finished pharmaceutical products, the NHS guideline recommends that the output reference flow should be reported both on a per mass and per tablet basis where applicable. The quantity and percentage of active ingredient should also be reported.

However, in order to achieve comparability, the function of the pharmaceutical should be reflected in the functional unit. Therefore, DDD is proposed as functional unit.

System boundary

The system boundaries describe the scope in terms of what process steps that shall be included in the system, and what can be excluded. The system boundaries are described in a system diagram (flow chart) and by specifying the included processes in each life cycle stage.

The scope of this PCR, and EPDs based on it, is defined in three levels:

- Level 1. Cradle-to-gate – Finished API (Active Pharmaceutical Ingredient)
- Level 2. Cradle-to-gate – Finished pharmaceutical product
- Level 3. Cradle-to-grave – Full life cycle for pharmaceutical products

Note: the levels build on each other; e.g. a completed Level 1 for API is required in order to complete Level 2 Finished Pharmaceutical Product.

Level 1 and Level 2 are divided into two stages, for the purpose of defining data requirements and for presentation of results:

- *Upstream processes*; from cradle-to-gate,
  i.e. includes all process steps from extraction of resources (cradle) to finished materials (gate)
- *Core processes;* from gate-to-gate,
  i.e. includes process steps from defined start (gate) to finished product (gate) in form of API or pharmaceutical product

Level 3 includes all stages of the life cycle and is divided into:

- Cradle-to-gate (Upstream and Core processes for Level 1 and Level 2)
- *Downstream processes;* from gate-to-grave, i.e. from finished product (gate) to end-of-life (grave)

Figure 10 below provides a schematic overview of the content of the different levels, and the division into Upstream, Core and Downstream processes. Each level is described in detail, by a system diagram and by included life cycle stages (see following subchapters).

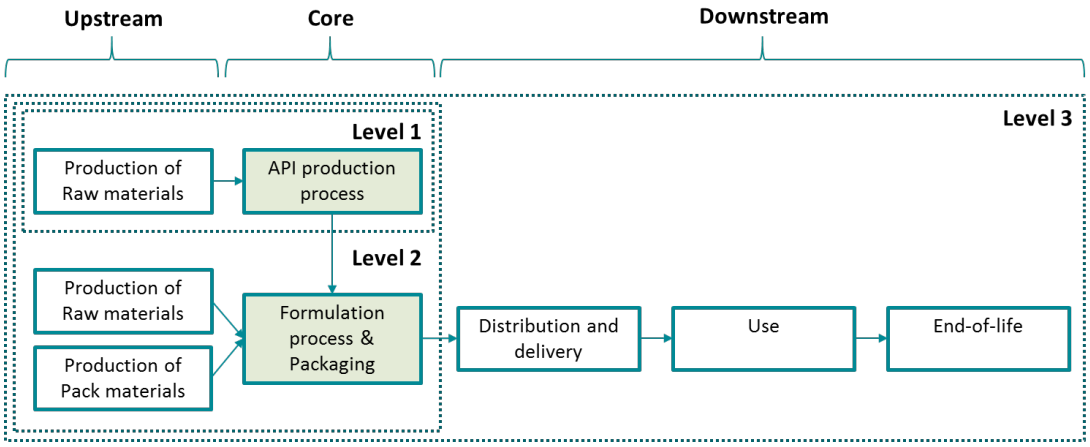


Figure 10 Overview of product life cycle and division into life cycle stages and different levels

The data for *core processes* shall be representative of both the actual production processes and of the site/region where the respective process is being performed.

For *upstream processes* generic data from e.g. international databases can be used.

All attributional processes in the life cycle shall be included. Also, some non-attributable processes shall be included as specified in the PCR.

An Attributable Process is defined as:

- Service, material, and energy flows that become the product, make the product, and carry the product through its life cycle.
- Examples of attributable processes may include manufacture of chemical feedstocks and solvents, production of energy used during processing and disposal of waste.

Non-Attributable Process is defined as:

- Processes and services, materials and energy flows that are not directly connected to the studied product because they do not become the product, make the product, or directly carry the product through its life cycle. However, they are needed for the production of the product.
- Examples of non-attributable processes may include production of chemicals used during cleaning, sterilisation and production of protective gear used by operators.

The division into Upstream, Core and Downstream is based on how the life cycle generally is defined for the purpose of PCRs, as defined in the PCR basic module. The definitions of attributable and non-attributable processes (above) are based on the NHS guideline.

The description of included process steps for Level 1-3 below is based on the NHS guideline, and has been adapted for the purpose of the PCR. In the adaptation a draft proposed division of process steps into Upstream, Core and Downstream processes have been created.

Note: In the PCR a distinction is made between "processes" and "flows".

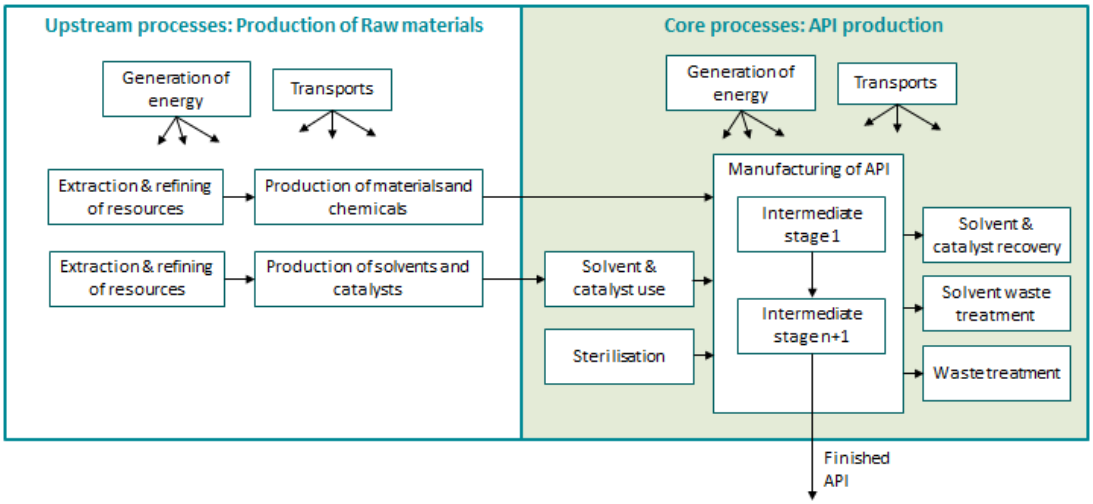
In this chapter, only "processes" are described, i.e. the processes along the life cycle needed to produce the product. Requirements in terms of what input and output "flows" to collect for the processes (e.g. material inputs, energy use, etc) are described in chapter "Data collection and data quality requirements" as well as in "Cut-off rules".

The requirements in the NHS guideline have therefore been adapted here, so that the system description only includes processes/process steps. Requirements concerning flows are available in the "Data collection and data quality requirements" chapter. For example; refrigerant leakage is classified as a flow (not a process).

Level 1 - System diagram and life cycle stages

In the EPD, the environmental performance associated with each of the life-cycle stages shall be reported separately.

Level 1 System diagram



Level 1 - Upstream processes

The following attributional processes are part of the product system and are classified as upstream processes:

- Production of raw materials and chemicals used as inputs to the core process. The production includes extraction, transports and refinement of resources.
- Production of solvent and catalysts used in the core process
- Generation of energy used in the upstream processes
- Transports between upstream processes
- *Treatment of waste generated in upstream processes*

The following non-attributable processes should be included:

- Production of the chemicals used for cleaning in the core process

Level 1 - Core processes

The following attributional processes are part of the product system and classified as core processes:

- Manufacturing and storage of the API (including all intermediate stages)
- Solvent and catalyst use and disposal
- Solvent recovery and incineration
- Generation of energy used in the core process
- Transports to and between core process steps
- Treatment of waste generated in the core process

The following non-attributable processes should be included in the product system:

- Sterilisation

Level 1 – Excluded processes

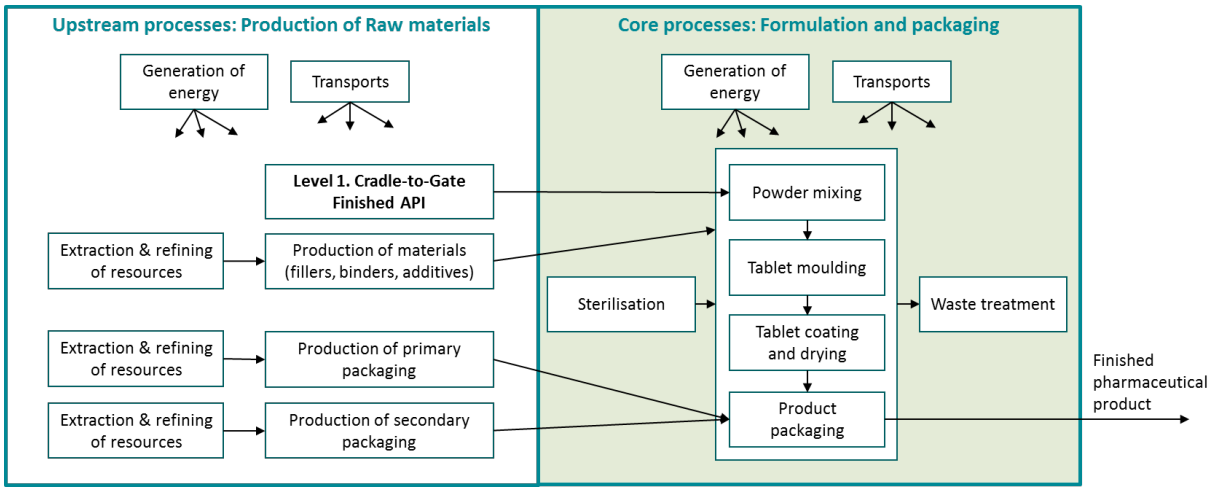
The following attributable and non-attributable processes shall be excluded from the product system:

- Packaging materials for raw materials & chemicals used in the core process
- Disposal of input packaging (eg IBCs, drums, pallets, etc)
- Production and disposal of consumables (eg gloves and protective clothing, filters, cartridges, etc)
- Manufacturing of production equipment, buildings and other capital goods.
- Business travel of personnel and travel to and from work by personnel.
- Research and development activities.

Proposed system content is adapted from the NHS guideline and is divided into Upstream and Core processes in line with the PCR basic module

Level 2 - System diagram and life cycle stages

Level 2 - System diagram



Level 2 - Upstream processes

The following attributional processes are part of the product system and classified as core processes:

- Production of raw material inputs to the core process (additives, fillers, binders etc.). The production includes extraction and refinement of resources and transports.
- Production of primary packaging material
- Generation of energy used in the upstream processes
- Transports between upstream process steps
- Treatment of waste generated in upstream processes

The following non-attributable processes should be included:

- Production of generic packaging materials
- Production of cleaning chemicals used in the core processes

Level 2 - Core processes

The following attributional processes are part of the product system and classified as core processes:

- Formulation and packaging processes for the pharmaceutical product
- Generation of energy used in the core process
- Transport to and between core process steps
- Treatment of waste generated in the core process

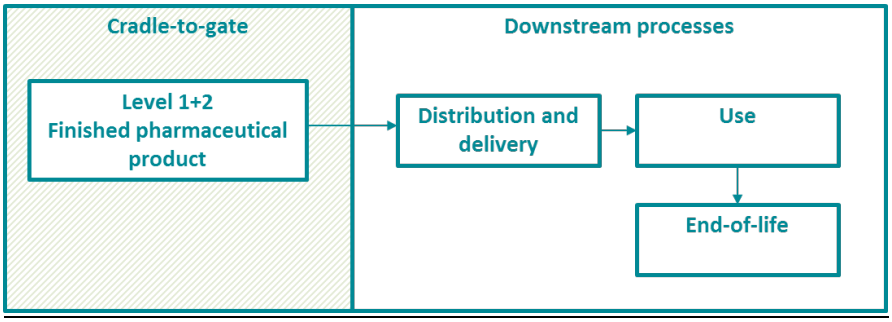
Level 2 – Excluded processes

See "Level 1 – Excluded process steps"; the same exclusions apply for Level 2.

Proposed system content is adapted from the NHS guideline and is divided into Upstream and Core processes in line with the PCR basic module

Level 3 - System diagram and life cycle stages

Level 3 - System diagram



Level 3 - Cradle to gate

According to requirements in Level 1+2 (see above).

Level 3 - Downstream processes

The following attributional processes are part of the product system and classified as downstream processes:

- Distribution and delivery
  - Transportation from preparation to an average retailer/distribution platform
  - Storage, including heating, cooling, lighting,
- Use, administration or consumption (use of product)
  - Production, distribution, consumption and disposal of *single use items*, e.g. syringe used to contain or administer (used to carry the pharmaceutical product into the patient or to directly apply it to the patient) the pharmaceutical product or to utilise the medical device
  - Use of equipment relating to the administration of pharmaceutical products or use of medical devices
  - Warming or cooling the product or carrier substance or liquids
  - Use and disposal of packaging

    - Transports of material and chemical inputs
- End-of-life - any wasted part of the product & packaging waste
    - Transport of waste product and packaging from the point of delivery to its point of final treatment - this should include intermediate transport stages, such as return of medicines or take-back of medical devices, etc
    - Waste handling and treatment processes
    - Degradation or destruction of materials at end-of-life (combustion or biodegradation)

The following non-attributable processes should be included:

- Distribution
    - Packaging used during transit and that may be used to speed delivery, protect or insulate product, including its disposal (eg pallets, plastic wrap and polystyrene insulation boxes)
- Use, administration or consumption
    - Non-commuting travel by the patient or the clinician to receive/collect/administer the pharmaceutical product or to utilise the medical device
    - Production, distribution and consumption of the carrier substances or liquids required to dilute, dissolve, hydrate, administer the pharmaceutical product or to utilise the medical device
    - Sterilisation and cleaning
- End-of-Life
    - Any pre-treatment required for the safe handling and management of waste/recyclable/ reused equipment
    - Production of spare parts/materials, and refurbishment and repair of reused devices

Level 3 – Excluded processes

The following attributable and non-attributable processes shall be excluded from the product system:

- Production of all capital goods; e.g. vehicles, infrastructure, buildings, machines,
- Patient transport to receive final delivery or administration of products (covered elsewhere in this document)
- Security requirements for product transportation
- All ancillary products and equipment, eg protective clothing etc
- The production, distribution, cleaning and disposal of multi-use equipment used to contain or administer the pharmaceutical product or to utilise the medical device
- Patient related aspects:
    - The consumption of food or drink by the patient
    - Health consequences for the patient
    - Other medicines, excluding required carrier substances or liquids, administered in tandem with the product of concern
    - Human metabolism
- Employee commuting
- Consequential effects of pharmaceutical release into the environment

Downstream processes have been adapted from the NHS guideline, in line with the PCR basic module.

For products where downstream impacts are minor in comparison with the "cradle to gate" impacts, the downstream parts may perhaps be simplified to more generic use scenarios.

However, specific data and scenario should be used for products where the downstream impact may be significant, e.g. where greenhouse gases are used in the administration of the product such as propellant gases in inhalation therapy.

Cut-off rules

Cut-off rules describe what flows that shall be included, and what can be excluded.

To reduce the amount of data required, it is possible to exclude immaterial inputs from the assessment. Immaterial inputs are defined as any materials that contribute less than 1% to the unpackaged weight of the product.

There are some limits to this 'cut-off rule', however:

- The total inputs excluded should not be greater than 5%.
- Inputs that are known to have a high GHG impact or are the primary purpose for manufacturing the product should always be included in the bill of materials.
- All APIs used should be included in the assessment regardless of its significance to the mass of the final product (because of their high GHG impact).

A screening assessment should be undertaken to identify any materials of high significance and determine the applicable materials to consider under the cut-off rules. Screening assessments and materiality tests provide valuable insight into the GHG emissions of a product and will allow prioritisation of data collection and efficient use of time and resource.

Description of cut-off rules is based on NHS guideline; no changes have been made.

Allocation rules

Allocation rules describe calculation rules for e.g. how to divide environmental impacts between different products produced at the same site, and how to handle re-use, recycling and recovery

Co-product allocation

An individual operation or whole site may produce multiple products. The following step-wise procedure shall be applied for such processes:

1. Allocation shall be avoided, if possible, by dividing the unit process into two or more sub-processes and collecting the environmental data related to these sub-processes.
2. If allocation cannot be avoided, the inputs and outputs of the system shall be partitioned between its different products or functions in a way that reflects the underlying physical relationships between them; i.e. they should reflect the way in which the inputs and outputs are changed by quantitative changes in the products or functions delivered by the system.
3. Where physical relationships cannot be established or used as the basis for allocation (or they are too time consuming), the rules described below shall be used in accordance with

what is the case for the specific process. For processes not listed the most suitable allocation procedure shall be used and documented.

Single API Manufacture
Where a single API is produced data should be collected describing inputs for the site, sub-site or process over a period of one year and divided by yearly production.

Multiple API Manufacture with Similar Market Value
Where multiple APIs or co-products are produced from the same process and data cannot be disaggregated, the total process inputs for a period of one year should be collected. Should all APIs and co-products from the process have similar value in the marketplace then the total mass of all products and co-products for the period of data collection should be used to allocate GHG emissions per product / co-product.

Multiple API Manufacture with Different Market Value
Where multiple APIs or co-products are produced from the same process and they have notably different market values, allocation should be undertaken on an economic basis(where co-products have nominal value, allocating on a mass of output basis is not an accurate method for apportioning process GHG emissions). Yearly process data should be collected and all products and co-products identified. The total value of all products and co-products sold should be calculated and yearly process data divided by this value.

Allocation for tablet manufacture
Where multiple tablets types are processed through the same production lines and sub-metering is not available (eg spray drying), allocation of process data is recommended. Allocation on the basis of product mass is the preferred approach to apportion process GHG emissions to different products.

The step-wise procedure for allocation is based on general LCA methodology and the PCR basic module.

The rules for allocation API and tablet manufacture are based on NHS guideline; no changes have been made.

Reuse, recycling, and recovery

The methodological choices for allocation for reuse, recycling and recovery have been set according to the polluter pays principle (PPP). This means that the generator of the waste shall carry the full environmental impact until the point in the product's life cycle at which the waste is transported to a scrapyard or the gate of a waste processing plant (collection site). The subsequent user of the waste shall carry the environmental impact from the processing and refinement of the waste but not the environmental impact caused in the "earlier" life cycles.

See more details in Data collection and data quality requirements

The general principle for allocation for reuse, recycling and recovery is based on the PCR basic module.

Data collection and data quality requirements

Data requirements describe specific requirements on the data that is used for different parts of the system, including requirements on data collection, assumptions, data quality etc.

Data shall be as specific as possible and shall be representative of the studied process.

Data on life cycle of materials or energy inputs are classified into specific data or generic data as follows:

Specific data (also referred to as "primary data" or "site-specific data")
data gathered from the actual manufacturing plants where product-specific processes are carried out, and data from other parts of the life cycle traced to the specific product system under study, e.g. materials or electricity provided by a contracted supplier that is able to provide data for the actual delivered services, transportation that takes place based on actual fuel consumption, and related emissions, etc., This is first-hand information, specific to the activity in question (e.g. kWh consumed by a process at an individual site, or an average across sites), collected internally or from the value chain. Specific data can be measured, calculated or modelled, as long as the result is specific to a process in the product's life cycle.

Generic data (also referred to as "secondary data")
Generic data are not collected from specific processes in the studied product's life cycle and may take the form of average, or typical, information about an activity (e.g. energy requirements and refrigerant losses for chilled storage) from a published study or other source. Generic data can be divided into:

- **selected generic data** – data from commonly available data sources (e.g. commercial databases and free databases) that fulfil prescribed data quality characteristics for precision, completeness, and,
- **proxy data** – data from commonly available data sources (e.g. commercial databases and free databases) that do not fulfil all of the data quality characteristics of "selected generic data".

Based on this classification, data requirements are defined in the following subsections, for different parts:

- Specific data - Principles and guidance
- Generic data – Principles and guidance
- Data requirements valid for all reporting levels - Energy, transportation and waste management processes
- Specific data requirements for each reporting level:
    - Level 1. Cradle-to-gate finished API
    - Level 2. Cradle-to-gate finished pharmaceutical product
    - Level 3 Cradle-to-gate finished pharmaceutical product – Specific data requirements
- Recommended databases for generic data

Specific data - Principles and guidance

As a general rule, specific data shall always be used, if available. It is mandatory to use specific data for the core processes, as defined above.

Specific data shall always be used for all processes under the control of the company (based on operational or financial ownership or control). Specific data should also be used as far as possible for processes in the value chain, where data is available and of sufficient quality. For upstream and downstream processes, generic data may be used if specific data are not available.

Any data used should preferably represent average values for a specific reference period.

Specific data shall also be representative for the specific market. If the same product is produced at more than one production site, the specific data shall cover at least 90% of total production for the specific market. In this case a weighted average of the involved production sites should be used. Deviations from this shall be justified.

Guidance for data collection

Specific data can be described in terms of raw materials data and process data:

- *Raw materials data* refer to the inputs of materials and chemicals included and consumed through the manufacture of the product and can typically be described as the bill of materials data.
- *Process data* refer to all other inputs and outputs that occur during the manufacturing process. These include energy and fuels consumed through the process, use of processing chemicals (e.g. solvents), emissions from the process and generated waste and discarded product. It is important to account for production efficiency (e.g. rework) when quantifying the inputs and outputs for a manufacturing process.

Raw material data can be collected from a number of sources and methods including:

- Operating and batch manufacturing instructions (process guides) for API manufacture
- Bill of materials data
- Financial systems used for procurement and supply monitoring
- Note that mass balances from processes and chemical equations should always be undertaken to ensure losses in the process as well as waste are accounted for.

For process data a number of possible data collection methods exist, including (in order of preferred approach):

1. direct measurement from process;
2. allocating site level data; and
3. theoretical calculations.

The general principles for specific and generic data are based on the PCR basic module, using parts adapted from the NHS guideline. The guidance for data collection is based on the NHS guideline

Generic data - Principles and guidance

Where specific data is not available or of insufficient quality, then generic data may be used. Generic data are usually less accurate than specific data, as they will relate to processes only similar to the one that actually takes place, or to an industry average for that process.

The following hierarchy for generic data is recommended:

1. Emission factors generated from average industry data and contained in life cycle inventory databases, industry association reports, government reports and that are compliant with ISO Life Cycle Assessment standards and have been critically reviewed;
2. Where unavailable, other existing peer-reviewed life cycle data from published life cycle studies or from proprietary packages should be used; and
3. Where an emission factor for a specific material input or process is unavailable, substitute data may be used - for example, substituting materials with similar manufacturing processes.

To classify generic data as "selected generic data", they shall fulfil selected prescribed characteristics for precision, completeness, and representativeness (temporal, geographical, and technological):

- the *reference year* must be as current as possible and preferably assessed to be representative for at least the validity period of the reported data
- the *cut-off criteria* shall be met on the level of the modelled product system
- the *completeness* in the data set should, in principle, cover all elementary flows that contribute to a relevant degree of the impact categories, Elementary flows are flows to and from the environment, e.g. emissions, resources
- the technological and geographical *representativeness* of the data should as far as possible reflect the actual technology and geographical area where the processes take place. They can take the form of e.g. weighted average of the actual process mix, best available technology or worst operating unit)". The electricity mix used in such parts shall be approximated as the official production electricity mix in the marketplace for electricity in the country of manufacture.
- Data shall have been calculated with book-keeping approach i.e. without system expansion and credits for any avoided processes

The hierarchy for generic data is based on the NHS guideline. The specification of "selected generic data" is based on the PCR basic module.

Data requirements valid for all reporting levels - Energy, transportation and waste management processes

Generation of energy

Specific data should be used for all energy generation under the direct control of the company (e.g. on-site generation of steam, heat, electricity, etc.).

For electricity used in core processes and when specific data is used in upstream processes the following apply:

- Electricity production impacts shall be accounted for in this priority:
  1. Specific electricity mixes as generated, or purchased, from an electricity supplier, demonstrated by a Guarantee of Origin (or similar, where reliability, traceability, and the avoidance of double-counting are ensured) as provided by the electricity supplier. If no specific mix is purchased, the residual electricity mix from the electricity supplier shall be used[70].
  2. National residual electricity mix, or residual electricity mix on the market
  3. National electricity production mix or electricity mix on the market.
- The mix of electricity used shall be documented, where relevant.

For electricity used in downstream processes the following apply:

- Use of electricity in the region/country where the product is used shall be accounted for in the following priority:
  1. National residual electricity mixes or residual mix on the market
  2. National electricity production mix or electricity mix on the market

  The mix of electricity used in the downstream processes shall be documented in the EPD, where relevant.

Requirements for electricity are based on the PCR basic module

Transportation

As a general rule, collection of specific data is required if the transportation stage is under the direct control of the company conducting the assessment. In this case, data shall be collected for actual transportation mode, distance and vehicle load. In the first instance, the fuel consumption per weight or volume capacity of the vehicle should be allocated to the product based on the weight transported. If these data are not available, the average fuel consumption of the delivery vehicle, the distance travelled, and the weight of transported goods can be used.

Specific data for transports should be collected as follows:

- *Upstream processes:* Transport of main parts and components along the supply chain to a distribution point (e.g. a stockroom or warehouse) where the final delivery to the manufacturer can take place

[70] The residual electricity mix is the mix when all contract-specific electricity that has been sold to other customers has been subtracted from the total production mix of the electricity supplier.

- *Core processes:* Transport from the final delivery point of raw materials, chemicals, main parts, and components (see above regarding upstream processes) to the manufacturing plant/place of service provision
- *Downstream processes:* The transport of the product to the customer shall be described and reflect the actual situation to the best extent possible. The following priority should be used:
    1. Actual transportation distances and modes.
    2. Calculated as the average distance of a product of that product type transported by different means of transport modes.
    3. If specific data cannot be obtained; generic data can be used as follows: Calculated as a fixed long transport, such as 1 000 km transport by lorry or 10 000 km by airplane, according to product type.

Requirements for transportation are based on the PCR basic module.

Waste management

In core processes, the waste treatment processes of manufacturing waste should be based on specific data, if available. If specific data is not available generic data can be used.

End-of-life profiles should be established for:

- non-hazardous waste (e.g. packaging, non-hazardous manufacturing waste)
- hazardous and clinical waste (e.g. hazardous manufacturing waste, from administration in clinical setting)

The end-of-life profile approximates the proportions of each component that is reused/recycled/landfilled/incinerated/other. Consideration should be given to both the location and context of the point of waste arising in determining an appropriate end-of-life profile.

For an inventory that considers an 'average' product, rather than a specific country of use, consideration should be given to the weighted end-of-life profile across at least 80% of the product market.

To model the impacts depending on waste treatment method, the following apply

Incineration without Energy Recovery
Emissions associated with incinerating wastes where energy recovery does not occur should be calculated based on the carbon content of the material

Incineration with Energy Recovery
Emissions associated with incinerating wastes where energy recovery occurs should be included in the GHG inventory as described above. The amount of energy recovered and exported for useful purpose (eg sold to the national grid or used for district heating) should be quantified and reported, together with any key assumptions. The avoided emissions from producing an equivalent quantity of electricity or heat by conventional means should be calculated using a system expansion approach.

Landfill of Inert Wastes
Emissions associated with non-biodegradable wastes to landfill can usually be assumed to be zero, as no GHG will be released from this material, and processing GHG emissions at a landfill site will be minor.

Landfill of biodegradable Wastes
Where landfill is not an important part of the product system, emissions can be estimated using the material-specific factors in Annex 9 of the Defra/DECC reporting guidelines[71].

Where considered potentially significant, an estimate of 50% of the carbon contained within the material could be assumed to be released as carbon dioxide, and these emissions should be added to the product GHG inventory (reported separately). These emission factors are also based on an infinite time period and so assume that all the carbon within the waste material degrades. This is a conservative assumption and is reasonable in this context – but should be noted within any inventory reporting.

Where landfill is an important part of the product system, a more detailed estimate should be sought.

Requirements for waste treatment are based on the NHS guideline

Specific data requirements for reporting level 1. Cradle-to-gate finished API

Core processes

The manufacture of an API may contain many intermediate chemical transformations. Specific data should be collected for all intermediate stages in the manufacturing of the API. The collected data should include process emissions from synthesis and any refrigerant leakage associated with product manufacturing.

If specific data cannot be collected, intermediate transformations can be approximated by proxy generic data, using the following approach. Method 1 is the preferred approach. Using either method should be considered as having a low data quality score.

Method 1: Theoretical Approximation
The initial chemical feedstock should first be identified followed by the chemical processes that the API undergoes during manufacture. These data should be readily available through either the company R&D activities or through the detailed operating instructions. Theoretical calculations based on thermodynamics and chemical equations can be undertaken to calculate each intermediate process stage. The intermediate process stages can be combined with the chemical feedstock to develop an emission factor for the intermediate product entering the company's direct operations.

Method 2: Chemical Transformation Scaling Method
Should the intermediate process stages not be known, or it is not possible to calculate the theoretical process GHG emissions, a scaling system can be applied. The initial chemical feedstock should still be identified and approximated. Once the number of intermediate chemical transformations is identified, a scaling factor can be applied per chemical transformation to produce an estimate for the API.

Upstream processes

Typically, a chemical is purchased as a feedstock to begin the organic synthesis process. A company may only directly undertake some of the intermediate processes to manufacture the API,

[71] http://www.defra.gov.uk/environment/economy/business-efficiency/reporting/

but the initial base feedstock used should always be determined regardless of the stage at which the company begins processing. For simple chemicals, effort should be made to collect specific data as far up the value chain as possible.

To approximate purchased chemicals from generic data sources, the following hierarchy should be used:

- an exact match;
- similar chemistry;
- combination of constituent chemicals for synthesis (eg using stoichiometric calculations with acrylic acid and ethanol data to approximate ethyl acrylate); and
- chemical source category (eg organic versus inorganic chemicals).

The description is based on the NHS guideline

Specific data requirements for reporting level 2. Cradle-to-gate finished pharmaceutical product

Core processes

Specific data shall be used for all stages in the formulation and packaging processes. The collected data should include sterilisation energy and associated chemicals and any refrigerant leakage associated with product manufacturing.

Upstream processes

Production of excipients (eg Fillers, Binders, Additives and Coatings)

Specific data should be collected if the manufacture of these materials is under the direct control of the company, or where data collection is possible from e.g. suppliers.

Generic data sources may be used where specific data are not available. The age, geography and technology representativeness of the generic data should be considered and amended to be product specific where appropriate.

The quality of chemicals and excipients should be considered when using generic data sources and a scaling factor should be considered for industrial grade emission factors when pharmaceutical grade chemical quality is required.

Should excipient generic data be required but not available, guidance for chemical feedstock approximation may be applicable. Of particular relevance is the Finechem tool for approximating petrochemical-based materials.

Production of packaging materials:

Specific data shall be used for the consumer packaging production if it is under the direct control of the organization or if the environmental impact related to the consumer packaging production is more than 10% of the total product environmental indicators. In other cases, generic data may be used.

If packaging is manufactured off-site, some specific data are still recommended including:

- Type/weight of materials used in primary/secondary packaging;
- Weight and material type of constituent components (eg leaflets);
- Source location of packaging;
- Recycled content of all packaging.

The description is based on the NHS guideline

Specific data requirements for reporting level 3 Cradle-to-gate finished pharmaceutical product

Downstream

Use:

Data for the use stage are usually based on scenarios, but specific data should be used when available and relevant. Data on the pollutant emissions from the use stage should be based on documented tests, verified studies in conjunction with average or typical product use, or recommendations concerning suitable product use.

Collection of specific data is recommended if the administering of the pharmaceutical product or the use of medical devices is under the direct control of the company conducting the assessment.

The following information may be required when collecting specific data to determine the use profile of a product or device:

- Quantities of single use items consumed.
- Energy consumption of equipment.
- Mode of transport, distances and fuel consumption of vehicles under the direct control of the company conducting the assessment.
- Quantities of carrier and dilution products consumed.
- Release of gases and refrigerants.

Production, distribution, consumption and disposal of single use items

Single use items include e.g. syringes. Sources of data include published carbon footprints or life cycle assessments of the single use items. In the absence of published studies or data from suppliers, an estimate can be made using the mass and material composition of the single use item

Energy use of equipment used to administer or store pharmaceutical products

Equipment to administer pharmaceutical products include e.g. pumps. The energy consumption can be estimated by multiplying the specified power rating of pump equipment by the specified time required to administer the product. The impacts from generation of the used energy shall be modelled in accordance with the data requirements for energy (above)

End-of life

Where companies directly operate, or coordinate take-back schemes for unused pharmaceuticals or end-of-life/reused medical devices, they should collect specific process data on the operation of that scheme; including rates of take-back, logistics, refurbishment requirements, etc.

Recommended databases for generic data

Recommended databases for generic data for different processes are listed below.

Production of chemical feedstocks and solvents:

- Ecoinvent
- US LCI;
- ILCD; and
- International Journal of LCA.

Should the relevant chemicals data not be available through these sources, or other life cycle inventory databases, a software tool called Finechem has been developed by ETH Zurich may be used to estimate GHG emissions from chemical manufacture. To effectively use the Finechem software tool, knowledge of chemistry and chemical structures is beneficial.

For disposal of solvents, the disposal process can be modelled based on generic data sources from average data sets. One useful example is the Ecosolvent tool developed by ETH Zurich. Ecosolvent is an LCA tool that allows for various waste solvent treatment methods to be assessed for user-defined waste solvent mixtures. This model can be applied for distillation, incineration and waste water treatment technologies to approximate an emission factor for waste solvents, and pre-treatment impacts can be accounted for in the process

Production of excipients

- US NREL LCI (http://www.nrel.gov/lci/)
- ELCD (http://lca.jrc.ec.europa.eu/lcainfohub/datasetArea.vm)
- Ecoinvent (http://www.ecoinvent.org/)

Should excipient generic data be required but not available, the guidance for chemical feedstock approximation may be applicable (see chemical feedstocks above)

Production of packaging materials

Possible sources of generic data for packaging materials include:

- Inventory of Carbon and Energy (publically available) (http://opus.bath.ac.uk/12382/)
- Plastics Europe (http://www.plasticseurope.org/plastics-sustainability/eco-profiles.aspx)
- European Aluminium Industry (http://www.alueurope.eu/en/environment-health-safety/lca/)
- Ecoinvent (http://www.ecoinvent.org/)

Energy recommendations for packaging assembly can be approximated based on generic data sources on a mass basis of packaging, and should be included when assessing packaging impacts. Possible sources for these data include:

- Ecoinvent (http://www.ecoinvent.org/)
- International Journal of LCA (http://www.springerlink.com/content/0948-3349)

The above list is based on NHS guideline. Note that more detailed specification will be needed to secure comparability in assessments, e.g. same generic data sources should be used to model impacts for specific chemicals, etc.

Impact categories and impact assessment

Impact categories and impact assessment describes what environmental impacts that shall be included and reported. This also includes specifying which characterisation factors (sources and version) that shall be used in the impact assessment.

The potential environmental impact per declared unit for the following environmental impact categories should be reported, divided into core, upstream and downstream module:

- Emission of greenhouse gases (expressed as the sum of global warming potential, GWP, 100 years), in carbon dioxide (CO2) equivalents.

The 100-year time horizon global warming potentials (GWP) from the IPCC Fifth Assessment Report, 2014 (AR5) shall be used. For more information, please see the IPCC website (www.ipcc.ch). The use of the latest (AR5) values is recommended.

Note: As the project has decided to start with Carbon footprint, only climate is included in this PCR "embryo". Other impact categories such as resource use, acidification etc., have therefore been excluded.

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