



A perspective from De Soete *et al.* by Ghent University, Johnson & Johnson, GlaxoSmithKline, the Sustainable Healthcare Coalition and the American Chemical Society.

Challenges and recommendations for environmental sustainability assessments of pharmaceutical products in the healthcare sector

With a range of methodologies to ensure a broad stakeholder coverage, this work is reflecting on the efforts towards environmental sustainability assessment of pharmaceutical products. Next, it identifies future key action points and proposes a set of recommendations by and for the sector to steer further development in order to support decision making processes.

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Challenges and recommendations for environmental sustainability assessments of pharmaceutical products in the healthcare sector†

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With healthcare representing a significant portion of the global economy, it is important to be able to understand the environmental impacts of this industry due to its size and nature of its operations. Interviews with people who have intimate knowledge of the healthcare industry indicate that significant efforts and advances have been made over the past ten to fifteen years in developing environmental impact assessment methods and tools tailored for the sector. These methods and tools have been important in helping to improve the overall environmental sustainability of the sector. However, comprehensive literature searches reveal that only a limited portion of the environmental impact assessment work has been published and/or is publicly available. This lack of visibility to the full scope of environmental impact assessment methods and the results of application of those methods can impair the advancement of these methods. To help facilitate further advancement of environmental assessment methodologies in the healthcare sector, Ghent University and the European Commission's Joint Research Centre, Sustainability Assessment Unit (JRC IES SA) undertook a study to map current challenges in conducting assessments, identify best practices in assessing and advancing the state-of-the-art, and to develop recommendations and priority action points based on the study learning. The study was accomplished through: (1) conducting a thorough literature review; (2) broad engagement of healthcare sector stakeholders, including industry, academia, NGOs, policy makers, GPs, patients, etc.; (3) execution of a stakeholder survey; (4) expert interviews; and (5) roundtable discussions with sustainability professionals in the field. Upon identifying the bottlenecks in current practices, four recommendations and key action points were determined: (1) the integration of the complete healthcare pathway within system boundaries; (2) the establishment of life cycle databases for pharmaceuticals and supplied resources; (3) the integration of LCA calculations directly into Enterprise Resource Planning (ERP) systems to work with primary data as much as possible; and, (4) the need to further harmonize developments in the field. The authors provide suggested actions to address the recommendations and propose this work as guidance to steer further research and developments in academia, industry and policy environments in order to serve and support decision making processes.

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Introduction

According to the WHO's Global Health Observatory, the worldwide total expenditure on health was 10.0% of the Gross Domestic Product (GDP) in 2013.¹ In Europe, the overall healthcare expenditure expressed as a percentage of the GDP increased from 8.2% in 2007 to 8.8% in 2012.² Following the European Commission's (EC) Directorate-General (DG) Health and Food Safety's European Core Health Indicators (ECHI), the public sector spending increased from 5.9% of the GDP to 6.6% in 2012.³ These are revealing and significant findings since public expenditures have only been decreasing in relation to the GDP since the economic crisis of 2009.⁴

Furthermore, the statistics of the DG for Economic and Financial Affairs reveal that public expenditure on health will further increase on average by 1.0 to 2.0% of the GDP across EU up to 2060.² When it comes to the private sector, the second most listed companies in the top R&D investing companies – for both EU and non-EU countries – are from the Pharmaceutical and Biotechnology sector.¹ In absolute numbers, the global pharmaceutical market almost tripled in the period 2001 to 2013, growing from around 390.2 billion US dollars in 2001 to 980.1 billion in 2013.⁵

In the US as well, the healthcare sector is a driver of economic growth, with spending on healthcare in 2012 reaching \$2.8 trillion, or 17% of the US GDP. However, the healthcare sector as any industrial activity is also a source of emissions that may adversely impact environmental and public health, some of them still in the process of being understood and quantified (e.g., pharmaceuticals in the environment).⁶ The current state of the healthcare industry offers significant opportunities for environmental efficiency improvements, potentially leading to reductions in costs, resource use, and waste without compromising patient care. However, limited research exists that can provide quantitative, sustainable solutions.⁷

The preceding paragraphs clearly show a continuing growth of the healthcare sector including the pharmaceutical industry. With an ever growing population and a growing share of elderly people, 'healthy living' and 'active aging' became priorities on several Strategic Agendas (SA) within the scientific research focus on health in e.g. the European Framework Program Horizon 2020 and the Knowledge and Innovation Community (KIC) on Health from the European Institute for Innovation and Technology (EIT).⁸ Not by accident, a parallel KIC was formed on Raw Materials (KIC RM), focusing on

technology development, mining and extraction innovations and recycling in order to tackle our finite resource supply.⁹ As it was depicted by Thomas Malthus and later by Dennis Meadows, we are facing an ever growing population with a finite supply of resources or raw materials, and as it happened before, innovation is key to continued and sustainable growth.^{8,10,11} Bearing that in mind, it is not hard to see that the growth of the healthcare sector and pharmaceutical industry and the focus on research and technology development are emerging and of ultimate necessity.

While Research & Development (R&D) and innovation is fostering growth, it should serve society in the decoupling of growth and raw materials extraction. Embracing sustainable development as the development that meets the needs of mankind preserving the needs of our future generations, both resource decoupling and impact decoupling become the inherent characteristics of sustainable development.⁸ This means that the decoupling of resource consumption and economic growth or prosperity on the one hand and decoupling of environmental impacts and economic growth on the other hand are key, implying resource efficient use of raw materials and technological innovation. There is thus an emerging need to evaluate whether or not investments in R&D and innovation projects (up to 40% of total revenue) in the healthcare and pharmaceutical industry from both private and public investors are sustainable.^{2,12}

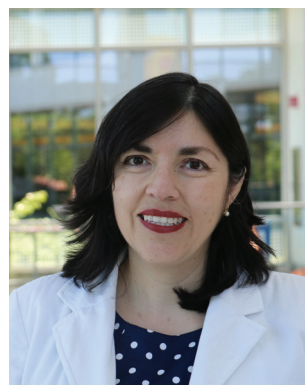
In the pharmaceutical sector, environmental metrics (e.g. Process Mass Intensity, Atom Efficiency, amongst others) have been developed over the last two decades to evaluate the environmental sustainability of chemical synthesis routes of Active Pharmaceutical Ingredients (APIs) (primary manufacturing), dosage form production (secondary manufacturing), packaging, distribution and logistics and the End-of-Life



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Concepción Jiménez-González

Conchita Jiménez-González has 25 years of experience in pharmaceuticals and chemicals. She has developed streamlined LCA analytic tools and computer modeling methodologies to guide business decisions. She is Program Lead at GlaxoSmithKline, where she has had roles of increasing responsibility, including Director of New Product Development, Director of Operational Sustainability; amongst others. She is an

adjunct professor at NCSU, an IChemE Fellow, serves in the ACS GCI's Governing Board, and was appointed to the EPA's Science Advisory Committee on Chemicals. Conchita holds a Ph.D. in Chemical Engineering; an M.S. in Environmental Engineering, and a B.S. in Chemical and Industrial Engineering.

phase (pharmaceuticals in the environment). Metrics can roughly be subdivided between process-oriented metrics and life cycle oriented metrics.^{11,13} Green chemistry principles started to create visibility within the sector with publications of Pfizer and GlaxoSmithKline (GSK) in the late nineties early 2000.^{14–29} In 2005, the formation of American Chemical Society (ACS) Green Chemistry Initiative (GCI) Pharmaceutical Roundtable (PR) was accomplished, whilst integrating more and more life cycle driven indicators in evaluation methods (e.g. Carbon Footprint, CF) together with Green Chemistry Metrics (GCM). Life Cycle Assessment (LCA) has become a widely used method to assess the environmental impact of pharmaceutical products.³⁰ The foundation of the UK's National Health Service (NHS) Sustainable Development Unit (SDU) in 2008 and the subsequent focus on the contribution of pharmaceuticals through the Coalition on Sustainable Pharmaceuticals and Medical Devices (CSPM) to the CF of NHS activities was recognised to be the next step towards elaborating different Life Cycle Impact Assessment Methods (LCIAMs).

Not too many, but some very comprehensive reviews have been written on the state-of-the-art in sustainability assessments for pharmaceutical products (APIs or dosage forms) by e.g. Constable *et al.* in 2007,¹⁵ Jiménez-González *et al.* in 2014³¹ and Kralisch *et al.* in 2015.³² However, whilst perfectly shaping the written state-of-the-art in sustainability assessments for pharmaceutical products, these reviews do not take into account several important aspects. First, the healthcare sector is an important contributor to take into consideration since pharmaceuticals only serve as a product within the complete healthcare pathway of a certain disease pattern. Many (especially chronic) treatment pathways do require quite some resources (e.g. General Practitioner, GP visits, therapy, hospitalization, *etc.*). Second, in a literature review, input data are commonly being processed from several published studies.

Unfortunately, a considerable amount of efforts made towards improving environmental sustainability may not have been published and are used internally for optimization purposes only. Hence, broader stakeholder coverage to include the voice of the industry, academia, NGOs, policy makers, GPs, patients, *etc.* is emerging. This paper takes the concept of reviewing and adding to the state-of-the-art through recommendations from and to the sector one step further.

The aim of this study, conducted by Ghent University and the European Commission's Joint Research Centre, Institute for Environment and Sustainability, Sustainability Assessment Unit (JRC IES SA), is to map current challenges in order to advance the state-of-the-art of environmental assessments, to share experiences and connect professionals and eventually to come up with recommendations and priority action points. This is accomplished through (1) a thorough literature review; (2) a stakeholder survey; (3) expert interviews and (4) roundtable discussions with sustainability professionals in the field (Fig. 1). In order to create a high leverage effect and a broad encouragement of the outcomes, a variety of stakeholder

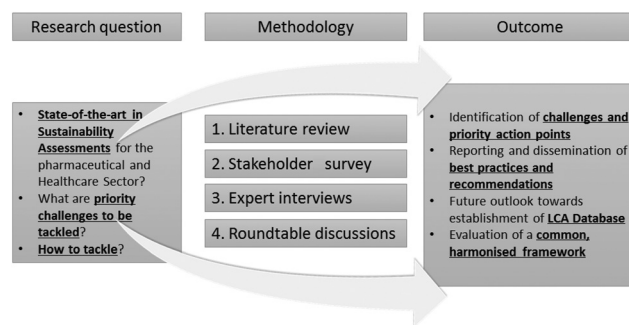


Fig. 1 Schematic representation of the study outline: (1) research questions; (2) methodologies and (3) envisaged outcomes.



Phil Dahlin

Philip Dahlin has over 25 years of experience in the environmental, health and safety (EHS) and sustainability fields in the waste and healthcare industries as well as in environmental consulting. Phil is the Global Director of Sustainability for Johnson & Johnson, where he oversees sustainability science and research, including LCA studies. He has worked with the UK's National Health Service's Sustainable Development Unit

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Jo Dewulf

Jo Dewulf is a full professor at Ghent University, Department of Sustainable Organic Chemistry and Technology. He focuses on resource consumption and efficiency analysis, relying mainly on thermodynamic principles and life cycle thinking. For his work, he obtained the prize of the Laureate of the Royal Academy of Sciences and Arts of Belgium in 2008. During 2013–2015, he worked as a senior scientist at the European

Commissions' Joint Research Centre on the sustainable use of natural resources including resource efficiency, criticality, supply resilience, *etc.* He holds a Ph.D., M.S. and B.S. in Bioscience Engineering.

communities were consulted: (1) private organisations; (2) policy and governmental research and decision support bodies and NGOs; (3) universities and research institutions; (4) sector federations, agencies and consortia and last (5) consumers (hospitals, pharmacists, patients and GPs).

Results and discussion

The results of this multidisciplinary set-up are presented in this section taking into account the different methodologies in gathering knowledge from the field. The more detailed methodological elaboration is given in the next section on Methodology.

Literature review

A thorough literature review, using the Web of Science™ from Thomson Reuters™ as a search engine was performed on the topics represented in Table 1. As a time window, publications ranging from January 1997 to April 2016 were considered. A complete, chronological list of relevant research papers, including citations, publication type, topic, journal ranking through Impact Factor (IF) and research field quartile is made available in ESI 1.† A short discussion follows below, highlighting the most cutting-edge and most cited articles as milestones within the field of sustainability assessments on pharmaceuticals within the healthcare sector.

Based on their number of citations and evaluation by experts (resulting from the expert interviews conducted in this project and further explained in the Methodology section), six milestone papers were selected (represented in bold in Table 1). These milestone papers follow the chronological development of Green Chemistry (GC), Life Cycle Assessment (LCA) and sustainable development in general in the pharmaceutical and healthcare sector for the past two decades. Following the parole of deductive sciences ‘scire est mensurare’ or ‘measuring is knowing’, the types of indicators used to measure the ‘greenness’ of fine chemicals and pharmaceuticals and their production routes and technologies have shifted from a process-oriented approach in the early nineties towards a life cycle or value chain approach with publications peaking as from 2010. In 2002, David Constable *et al.* published a review on the former current approaches towards metrics to Green Chemistry.¹⁷ In their review, four years after Paul Anastas and John Warner published their well-known 12 principles of Green Chemistry, Constable *et al.* evaluated the effective mass yield, the *E*-factor and the atom economy indicators and explored the potential of newly developed indicators at GlaxoSmithKline (GSK), one of the first pharmaceutical companies to invest in Green Chemistry and, a member of the American Chemical Society (ACS) Green Chemistry Initiative Pharmaceutical Roundtable (GCIPR).^{17–20} GSK evaluated the Reaction Mass Efficiency (RME) (the ratio of the sum of the product masses and the sum of the reagent

Table 1 References used for literature reviews per topical search criterion

Topic search criterion	Ref.
Sustainability assessment of pharmaceuticals	(Wernet <i>et al.</i> , 2009), ³³ (Jiménez-González <i>et al.</i> , 2010), ³⁴ (Schneider <i>et al.</i> , 2010), ³⁵ (Jiménez-González <i>et al.</i>, 2011a), ³⁶ (Jiménez-González <i>et al.</i> , 2013), ³⁷ (De Soete <i>et al.</i> , 2013), ²⁵ (Woodley <i>et al.</i> , 2013), ³⁸ (Szekely <i>et al.</i> , 2014) ³⁹
Sustainability assessment in healthcare	(Briggs <i>et al.</i> , 2003), ⁴⁰ (Martin <i>et al.</i> , 2009), ⁴¹ (Boholm <i>et al.</i> , 2014), ⁴² (Carmen Carnero, 2015), ⁴³ (Castro <i>et al.</i> , 2015a), ⁴⁴ (Castro <i>et al.</i> , 2015b), ⁴⁵ (Debaveye <i>et al.</i> , 2016), ⁴⁶ (Marsh <i>et al.</i> , 2016) ⁴⁷
Life cycle assessment of pharmaceuticals	(Jiménez-González <i>et al.</i> , 2000), ⁴⁸ (Jiménez-González <i>et al.</i> , 2004), ²⁰ (Curzons <i>et al.</i> , 2007), ¹⁴ (Kim <i>et al.</i> , 2009), ⁴⁹ (Wernet <i>et al.</i> , 2010), ⁵⁰ (Igos <i>et al.</i> , 2012), ⁵¹ (Alfonsín <i>et al.</i> , 2014), ⁵² (De Soete <i>et al.</i> , 2014), ⁵³ (Jiménez-González <i>et al.</i>, 2014), ³¹ (Perez-Lopez <i>et al.</i> , 2014), ⁵⁴ (Brunet <i>et al.</i> , 2014), ⁵⁵ (Ramamamy <i>et al.</i> , 2014), ⁵⁶ (Ott <i>et al.</i> , 2014), ⁵⁷ (Ott <i>et al.</i> , 2016), ⁵⁸ (Cespi <i>et al.</i> , 2015), ⁵⁹ (Kralisch <i>et al.</i>, 2015) ³²
Life cycle assessment in healthcare	(Campion <i>et al.</i> , 2012), ⁶⁰ (Thiel <i>et al.</i> , 2015) ⁷
Green chemistry related to pharmaceuticals	(Curzons <i>et al.</i> , 1999), ⁶¹ (Curzons <i>et al.</i> , 2001), ⁶² (Constable <i>et al.</i>, 2002), ¹⁷ (Haswell <i>et al.</i> , 2003), ⁶³ (Nisiwaki, 2003), ⁶⁴ (Thomas <i>et al.</i> , 2005), ⁶⁵ (Koel <i>et al.</i> , 2006), ⁶⁶ (Tucker, 2006), ⁶⁷ (Constable <i>et al.</i>, 2007), ¹⁵ (Fortunak <i>et al.</i> , 2007), ⁶⁸ (Khetan <i>et al.</i> , 2007), ⁶⁹ (Kuemmerer, 2007), ⁷⁰ (Alfonsi <i>et al.</i> , 2008), ⁷¹ (Cue <i>et al.</i> , 2009), ⁷² (Fortunak, 2009), ⁷³ (García-Reyes <i>et al.</i> , 2009), ⁷⁴ (Molina-Díaz <i>et al.</i> , 2010), ⁷⁵ (Broxterman <i>et al.</i> , 2011), ⁷⁶ (Hartman <i>et al.</i> , 2011), ⁷⁷ (Wernet <i>et al.</i> , 2011), ⁷⁸ (Jiménez-González <i>et al.</i>, 2011b), ⁷⁹ (Joshi <i>et al.</i> , 2011), ⁸⁰ (Soundararajan <i>et al.</i> , 2011), ⁸¹ (Kaur <i>et al.</i> , 2012), ⁸² (Ley, 2012), ⁸³ (Watson, 2012), ⁸⁴ (Ciriminna, 2013), ⁸⁵ (Dunn, 2013), ⁸⁶ (Federsel, 2013), ⁸⁷ (Leahy <i>et al.</i> , 2013), ⁸⁸ (Osorio <i>et al.</i> , 2014), ⁸⁹ (Rastogi <i>et al.</i> , 2014), ⁹⁰ (Banimostafa <i>et al.</i> , 2015), ⁹¹ (DeVito <i>et al.</i> , 2015), ⁹² (Gupta <i>et al.</i> , 2015), ⁹³ (M'Hamed, 2015), ⁹⁴ (Roschangar <i>et al.</i> , 2015), ⁹⁵ (Sullivan, 2015), ⁹⁶ (Tucker, 2015), ⁹⁷ (Voorhees, 2015), ⁹⁸ (Gallou <i>et al.</i> , 2016), ⁹⁹ (Borukhova <i>et al.</i> , 2016) ¹⁰⁰
Resource consumption related to pharmaceuticals	(Van der Vorst <i>et al.</i> , 2009a), ¹⁰¹ (Van der Vorst <i>et al.</i> , 2009b), ¹⁰² (Van der Vorst <i>et al.</i> , 2010), ¹⁰³ (Van der Vorst <i>et al.</i> , 2011), ¹⁰⁴ (Van der Vorst <i>et al.</i> , 2013), ²⁴ (De Soete <i>et al.</i> , 2014) ¹⁰⁵
Resource consumption related to healthcare	(Hatoum <i>et al.</i> , 1998), ¹⁰⁶ (Optenberg, 2002), ¹⁰⁷ (Alvarez <i>et al.</i> , 2004), ¹⁰⁸ (Daskalaki <i>et al.</i> , 2007), ¹⁰⁹ (Manca, 2008), ¹¹⁰ (Leekha, 2009), ¹¹¹ (Gonzalez-Cortes <i>et al.</i> , 2011), ¹¹² (Gagliardino <i>et al.</i> , 2012), ¹¹³ (Polatli <i>et al.</i> , 2012), ¹¹⁴ (Roggeri <i>et al.</i> , 2014), ¹¹⁵ (Castro <i>et al.</i> , 2015a), ⁴⁴ (Martyn <i>et al.</i> , 2015) ¹¹⁶
Carbon footprinting of pharmaceuticals	(Connor <i>et al.</i> , 2010), ¹¹⁷ (Gatenby, 2011), ¹¹⁸ (Lim <i>et al.</i> , 2013) ¹¹⁹
Carbon footprinting in healthcare	(Connor <i>et al.</i> , 2011), ¹²⁰ (Wormer <i>et al.</i> , 2013), ¹²¹ (Holmner <i>et al.</i> , 2014), ¹²² (Pollard <i>et al.</i> , 2014) ¹²³

masses), mass intensity (the total mass of materials used per mass unit of product), mass efficiency (the inverse of mass intensity, expressed in percent) amongst others. In contrast with the effective mass yield and the *E*-Factor (mass of waste per mass of product), “RME appears to be a useful metric for focusing attention away from waste towards the use of materials.” As such, it was highlighted that it would be more likely to strive for technology innovation with sustainable best practices at the level of a chemical reaction.¹⁷ The work of Constable *et al.* was included in the book of Alexei Lapkin in 2009, a piece that bundled the state-of-the-art in Green Chemistry (GC) metrics for measuring and monitoring sustainable processes.¹³ GSK actually set a corporate target aimed to significantly increase the mass efficiency of new pharmaceuticals, which could potentially halve the waste generated. At the same time, GSK performed a company-wide carbon footprint setting the corresponding targets for global warming potential. By that time, it was generally accepted that focusing on RME was not the way forward, but mass efficiency provided a good sense of the productivity of pharmaceutical processes. Jiménez-González *et al.* published the views of the GCIPR and its member companies in 2011.³⁶ The GCIPR submits that the Process Mass Intensity (PMI, the inverse of mass efficiency) as a key metric accounts for the total mass of materials (product and waste) per mass of product. Although mathematically PMI is no more than the *E*-factor + 1, it does include the raw materials into the equation, which by far have a larger life cycle impact than the waste generated. In addition, by breaking down the PMI to subcategories water, reactants, solvents and others, a process-based hotspot analysis revealed the very high burden of solvents (up to 56%) in the production of Active Pharmaceutical Ingredients (APIs). Next to the fact that the PMI can be broken down according to different types of resources (*e.g.* solvent PMI, water PMI) in order to determine hotspots for prioritization, it allows system boundary definitions towards a more Life Cycle Thinking (LCT) perspective. In contrast to RME, system boundaries can be expanded depending on the processes under analysis, instead of focusing on the reaction level. The fairly simple process-oriented PMI metric showed linear correlations with the Global Warming Potential (GWP) ($R^2 = 0.88$) and the Aqueous Mass Intensity (AMI) ($R^2 = 0.95$), revealing part of the reasons for its popularity in the pharmaceutical sector: an easy to calculate metrics correlating with societal impacts focusing on the process level.³⁶ Later, life cycle based metrics (carbon footprint, water footprint, acidification potential, photochemical ozone depletion *etc.*) were added to the PMI tool of the GCIPR to compute PMI, cumulative PMI and life cycle based metrics at once in streamlined assessments.^{37,59} Although there have been several LCA studies in pharmaceuticals and some streamlined LCA tools, a lot was to be learned from the earlier tools and techniques, such as the published Fast Life Cycle Assessment of Synthetic Chemistry (FLASCTM) tool from GSK.¹⁴ In April 2007, the GCIPR from the ACS published some key GC areas of which both research institutions and businesses acknowledged them as key priorities on the GC agenda. In

terms of importance, the GCIPR ranked the following processes to be intensified over the next coming years: (1) amide formation avoiding poor atom economy reagents; (2) hydroxyl activation for nucleophilic substitution; (3) reduction of amides without hydride reagents; (4) oxidation/epoxidation methods without the use of chlorinated solvents and eventually (5) safer and more environmentally friendly Mitsunobu reactions.¹⁵ Obviously, all aforementioned priorities were very much focusing on the API production. Four years later, the GCIPR published their key green engineering research areas, which include more general sustainability priorities in the field of pharmaceutical manufacturing. It was agreed upon by the Board of associated companies to focus on (1) continuous processing; (2) bioprocesses; (3) separation and reaction technologies; (4) solvent selection, recycle and optimization; (5) process intensification; (6) integration of LCA; (7) integration of chemistry and engineering; (8) scale-up aspects; (9) PMI and (10) mass and energy integration (process intensification).⁷⁹

It was not until 2014 that two publications (a tutorial and review) were made in the field of LCA related methodological advances in the pharmaceutical sector. In 2014, Jiménez-González and Overcash published “The evolution of life cycle assessments in pharmaceutical and chemical applications – a perspective”,³¹ with a strong focus on the challenges faced with in order to generate the required Life Cycle Inventory (LCI) and using the resulting LCA output in decision making processes. Furthermore, it proposes a series of emerging developments within LCAs used for decision making in the fine chemical and pharmaceutical sector. For the first time, compiled from a significant amount of literature, the issue of obtaining appropriate LCI data was prominently recognized as challenge number one. The second challenge that was identified is effectively applying LCIA insights (especially the way we translate them to Multi-Criteria Decision Making (MCDM)).³¹ In the tutorial review by Kralisch *et al.* in 2015, more methodological aspects are touched upon.³² A very important one to add value in screening portfolios or development options on environmental sustainability is simplifying LCA and coupling LCA with other assessment methods (*e.g.* Life Cycle Costing – LCC – or risk assessment for nanomaterials) for MCDM in early stage development. Alternative energy sourcing, green solvents and introducing flow remains key as a hybrid form of the principles of GC and process intensification.³²

It has only been very recently that the scope of environmental sustainability assessments in the pharmaceutical industry was extended to the complete healthcare pathway, accounting for more unit operations (*e.g.* GP visits, hospitalisation, *etc.*) than just the production of the medicine. From a life cycle perspective, looking at functionalities and the delivered value, it is required to expand boundaries to the complete healthcare pathway. The value delivered by a healthcare company is human health, a therapeutic treatment, not just a tablet or a cream. This value should thus be reflected in the functional unit. For some disease patterns (*e.g.* psychiatric diseases), requiring hospitalisation for a longer time, medical

devices, *etc.*, the healthcare pathway dwarfs the impact of the drugs. This raises awareness on the fact that hospitals can both from an economic and environmental sustainability point of view be important hotspots in those value chains. Other types of diseases can be treated with mainly drugs without much extra healthcare resources. Depending on the targeted disease (chronic or acute) and the care pathway, the results may vary significantly.⁴⁶ Other important aspects of the care pathway can be advanced drug delivery devices or safety devices for safe injection (safe needles, *e.g.* for diabetes treatment). The same reasoning is applicable to smart medical devices (*e.g.* companion diagnostics, insulin pumps, *etc.*) on to the road towards personalised medicines. The work of the Sustainable Development Unit (SDU) of the British National Health Services (NHS) with its Coalition on Sustainable Pharmaceuticals and Medical Devices (CSPM) on “Care Pathways: Guidance on Appraising Sustainability” at the end of 2015 opened doors for a more complete assessment taking into account other services throughout the value chain of a certain care pathway, reaching out to the healthcare sector in general. This work was supported by the CSPM core members NHS England, the Public Health Ministry of England, AstraZeneca, Boehringer Ingelheim, Baxter Healthcare, GlaxoSmithKline (GSK), Johnson and Johnson, Medtronic, Novo Nordisk and Environmental Resource Management (ERM).¹²⁴

Expert interviews

Many of the aforementioned challenges and focus points were taken up as key issues/questions in the expert interviews that were conducted during this jointly performed study between Ghent University and the European Commission's Joint Research Centre. The next paragraphs will highlight the visions and best practices obtained from the expert interviews according to four predefined discussion topics.

Scoping, sourcing, and added value of performing environmental sustainability assessments

The main driving force to conduct sustainability assessments is unanimously agreed upon to be twofold: (1) internal process optimisation, (2) external communication towards stakeholders. The hotspot analysis of environmental impacts (especially resource based) throughout the value chain seems a sound base to identify optimisation potential, often in terms of process intensification (*e.g.* batch to continuous manufacturing, process flow integration, *etc.*), while for external communication aspects emission-based indicators are more popular (*e.g.* carbon footprint). Next to the two aforementioned drivers, sustainability attributes are helpful in the Design to Value (DtV) process to make any enterprise more competitive and more efficient in total cost and resource efficiency.

When it comes down to sustainability assessment strategies, the upcoming trend in the pharmaceutical and healthcare sector is the evaluation of healthcare pathways as a whole, instead of focusing on the stand-alone medicine as a product. Expanding the system boundaries from the product level (man-

ufacturing) to the product-service level (healthcare pathway, treatment) was found to be the way forward towards assessing the environmental burdens coming with the real value delivered by the sector: human health. Another strategic action towards including environmental sustainability in design processes (so called Quality by Design, QbD) is the inclusion of sustainability attributes and metrics in the development of decision trees and stage-gating processes.¹²⁵ While streamlined LCA (*e.g.* FLASC tool¹⁴ and De Soete *et al.*, 2014⁵³) is more and more being applied in early research phases together with qualitative measures (*e.g.* preferred solvents, toxic substance evaluation, *etc.*), full-blown LCA is used for optimizing case studies in retrofitting or for next generation medicines.

In terms of sourcing and quality assurance of outsourced LCAs to third parties, a lot of private entities see value in co-operating with universities and knowledge institutions in general for internal optimisation purposes. Universities are judged to be in front of the pack related to knowledge development and delivery of wanted profiles to the industry. Outsourcing to third party consultants is generally done for attributional LCAs and for benchmarking or sector wide purposes. In this case, often a quality check or intermediate reporting is performed between the Life Cycle Inventory (LCI) and the Life Cycle Impact Assessment (LCIA), falling back on the very iterative character of an LCA. Only a minor share of the pharmaceutical companies and shareholding entities in the Value Chain (VC) of the healthcare pathway perform LCAs internally, possibly putting a thread on central data management of LCIs. In quite some cases, when LCA studies are being outsourced without clear instructions or Execution Requirements (ERs) on how exactly to report the LCI(A) results, the impact assessment might be presented without clear insights into the structure and modelling of the LCI because there is a tendency that the LCI is not seen as an important outcome of the LCA in general. Organisations should specifically require the LCI results if they want to manage Life Cycle Inventory data of their products and processes internally.

Current shortcomings in LCA methodologies to support business and policy decision making

Some current shortcomings of LCA methodologies to support business and policy decision making with focus on the pharmaceutical and healthcare sector are represented below. These were gathered from interviews with the experts involved in this research.

- **Stakeholder involvement:** In light of improving data quality and enhancing the use of primary Life Cycle Data (LCD), both upstream and downstream Supply Chain (SC) actors should be taken into account. Upstream suppliers represent *e.g.* fine chemical producers, base chemicals, building blocks (Small Molecules, SM); feeding media, resins, disposables (Large Molecules, LM) and delivery devices and packaging suppliers. Downstream actors are *e.g.* logistic suppliers, hospital networks, wholesalers, national health services and in the end the patients. Other actors that might be considered in a

full healthcare pathway system are patient federations, General Practitioners (GPs), *etc.*

- **System boundaries:** A clear shift is trending from product systems to product-service systems. The very same is valid in the pharmaceutical/healthcare sector. More and more companies are extending the system boundaries of their LCAs. Embracing the full treatment pathway (with hospital visits, GP visits, *etc.*) in a healthcare system is shaping a more comprehensive picture of the burdens and benefits exerted at the level of the three areas of protection in LCA. This includes sophisticated safety and drug delivery devices, companion diagnostic devices, *etc.* The system boundaries need to be aligned with the research question that needs to be answered, and sometimes these are not thoroughly planned.

- **Streamlined LCA:** Fast screening methods and streamlined LCA methods are increasingly used in early stage assessments at low Technology Readiness (TRL) levels. Integration of LCA tools into existing engineering or Enterprise Resource Planning (ERP) systems seems to be the way forward to generate LCA results in a fast way at the desirable stage-gates of development.

- **Communication:** Outreaching with midpoint results is still a difficult concept for non-LCA experts, while endpoints could be easier to understand (*e.g.* DALY concept) but are less reliable in terms of uncertainty. Optimisation potential should be translated towards specific, prioritised key actions to enhance the value for decision makers.

- **Efficacy:** The primary focuses of healthcare providers are efficacy, compliance and safety for the patient. A major challenge is to include these aspects in LCAs. Bioavailability is typically decreasing for new, innovative compounds since they tend to be more and more complex. Through the study of clinical trials phase one, two and three, the bioavailable fraction of API intake can be taken into account in the Functional Unit. However, the transition from the inclusion of blood levels (instead of kg API or one tablet) to the treatment effect, taking into account the efficacy for the patient is challenging.

- **Pharmaceuticals in the environment:** Unfortunately, very little is known about what happens with pharmaceutical residues after the use phase of the product. For some pharmaceuticals, characterisation factors were established through exposure, fate, effect and damage factors.^{52,126} The PHARMAS FP7 project is one of the few projects dealing with the issue of ecological and human health risk assessments of antibiotics and anti-cancer drugs found in the environment. While fate and exposure factors of APIs could reasonably well be derived, identifying and measuring metabolites remains a future challenge.

- **Lack of Life Cycle (LC) Data:** It has been identified that the lack of primary process data to construct Life Cycle Inventories (LCIs) is one of the most important bottlenecks in LCAs of pharmaceutical products. The combination of the high added value of products, confidentiality, Intellectual Property Rights (IPR) and competitiveness makes Business to Business (B2B) data sharing along the value chain difficult without independent, objective third parties. As a result, the

next paragraph deals with recommendations to the sector on how to tackle data unavailability.

Tackling data unavailability from suppliers and vendors through the value chain

The general consensus on data sharing was reached amongst the experts is that they clearly see the benefits of sharing primary data, especially through the supply chain wrapped-up in business models engaging the *n*-*x* suppliers as well. However, the sector is carefully observing what downsides might be. Every data point published can be used by scouting/accounting agencies for benchmarking organisational behaviour and analysis of business results calculating life cycle inventories back to monetary flows. Therefore, transparency through the SC should be carefully provided, safeguarding the competitive advantage of every individual SC actor. Possible measures to be taken are the use of black box data models through the use of so-called system processes in LCI instead of unit processes, working with a third party database provider such as a sector federation, *etc.* Primary data should be used as much as possible, secondary data can be obtained through proxies, modelling tools (*e.g.* Finechem, FLASCTM) and databases. For the use of secondary data, the sector would benefit from fine chemical/pharmaceutical entries of solvents, building blocks, reagents, excipients, packaging materials, *etc.* in life cycle databases. When asking who should be the host of such a database, the sector prefers a third party such as the European Federation of Pharmaceutical Industries and Associations (EFPIA) or the Sustainable Procurement in the Health Sector (SPHS) Secretariat from the United Nations Development Program (UNDP). In addition to enhancements on data availability and relevance, the systematic inclusion of uncertainty and sensitivity analysis is strongly recommended, particularly as the LCI and LCA, as discussed above, by definition incorporate large uncertainties. Although the aim is to enhance the quality of the assessments, without uncertainty and sensitivity analysis, decisions made using LCA could be less than optimal. As a final remark, the experts mentioned that time and commitment are probably the two biggest hurdles to establish such a system today.

Standardisation and harmonisation of methodologies within the sector

As a last discussion topic touched upon during the expert interviews, standardisation and harmonisation of both LCI and LCIA methodologies within the healthcare sector were questioned. As will become clear from the stakeholder surveys as well, most used standardised guidelines for conducting LCA are ISO 14040/44, ELCD, GHG Protocol PAS 2050, Bilan Carbone, NHS Carbon Footprint Guidance for Pharmaceuticals, the Medical Devices and the World Business Council (WBC) Sustainable Development Guidelines, BSI for consumer goods and the MEASURE Roadmap for applying LCA/LCM in innovation projects. The choice merely depends on the market to be served (Bilan Carbone for France, NHS Guidance/BSI for the UK, *etc.*) which shows the need for a stan-

dardised method, especially for LCIA, that is recognized by all markets. The general Product Environmental Footprint (PEF) guidelines of the European Commission were tested by several pharmaceutical companies and the feasibility of using the guidelines was discussed during the interviews. The main drawback is the very diverse impact of pharmaceutical products with the aim at defining Product Category Rules (PCRs). Different studies have indicated a very large range in all impact categories due to a very diverse synthesis of APIs, biotechnological drugs, *etc.* A recommendation would be to find a feasible aggregation of drug types into product categories where sub-ranges are fairly limited. The industry stresses the importance of having this diversity within medicinal treatments, especially when dealing with companion diagnostics when medicines will be tailored to the specific genetic information of the patient. The authors would like to make the remark here that these ranges will tend to decrease when more LCI data are available. The LCI and impact assessment issue is inherently connected to each other and is to be seen as a major future challenge.

Stakeholder survey

As a third technique to gather state-of-the-art and ideally to come up with new insights and best practices not to be found in the scientific literature, the authors have sent out stakeholder surveys to five subcategories of stakeholders that were to be questioned according to the experts: (1) private organisations; (2) policy, governmental (research) bodies & NGOs; (3) university/research institutions; (4) sector federations/consortia and (5) consumers (hospitals, pharmacies, patient organisations, physicians). 344 potential participants were invited over the different stakeholder subcategories. However, several people conducting different roles within one legal entity were approached while almost every entity has sent in an aggregated entity vision or response, which was a good approach for gathering different visions from sustainability teams, product stewardship teams, compliance, *etc.* Unfortunately, we did not receive any response from the consumer category, despite three reminders. As a result, this category was left out of consideration, ending up with a total of 340 invitees. Of these 340 participants, 174 were unique identifiers, yielding a response rate of 24% (41 responses). Table 2 provides a more detailed analysis of the involved stakeholder groups, the amount of

individual invitees, the amount of legal entities consulted (aggregated invitees), the absolute amount and percentual aggregated responses per legal entity and finally the response rate per invited legal entity.

The ratio of $\frac{\text{Individual invitees } [\#]}{\text{Aggregated invitees } [\#]}$ is defined as the aggregation ratio per stakeholder group and is visualised in Fig. 2. The rather low relative response (%) (*cf.* Fig. 3b) of policy, governmental (research) bodies and NGOs compared to the response rate per invited entity (resp. 12% and 22%) is partly due to a large aggregation ratio (3.5) compared to the average (1.9) which might have had a negative effect on the responsiveness (*cf.* Fig. 2). Next, feeding into scientific surveys is probably of lower priority for policy makers. The opposite is valid for universities and research institutions (1.3), which can be considered to be more active and front running in developing and disseminating on LCA methodologies as well, partly explaining the high response rate. The response rate per invited sector federation or knowledge consortium was not expected to be only 4%. A reasonable explanation for this low number is that the authors reached out to the European Sector Federations EFPIA and the sector federations of the member states, who are either not that active in this field and/or were engaged to discuss this matter at the level of the overarching EFPIA. It was found to be very hard to engage consumer (patient) organisations. Of the 2 overarching entities approached, none of them

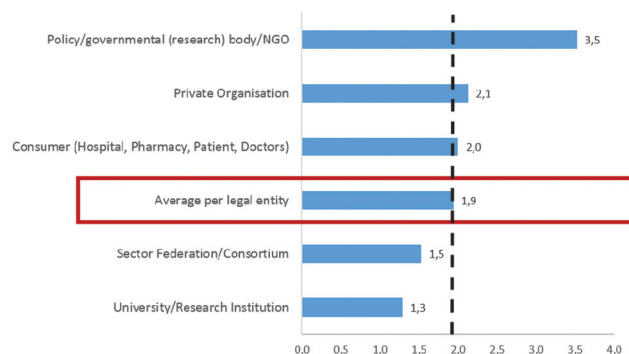


Fig. 2 The x-axis represents the aggregation ratio per stakeholder group (with an average of 1.9) defined as the amount of invitees divided by the amount of aggregated invitees. The y-axis represents the different stakeholder groups.

Table 2 Stakeholder invitation statistics and response rates: (1) individual invitees (#): absolute amount of invited individuals per stakeholder group; (2) aggregated invitees (#): amount of different legal entities consulted; (3) aggregated responses (#): amount of different legal entities responding; (4) relative responses (%): aggregated responses divided by total responses (41); (5) response rate per invited entity (%): aggregated responses divided by aggregated invitees

Stakeholder group	Individual invitees (#)	Aggregated invitees (#)	Aggregated responses (#)	Relative responses (%)	Response rate per invited entity (%)
Private organisations	119	56	17	41	30
Policy, governmental (research) bodies & NGOs	81	23	5	12	22
University/research institutions	27	21	16	39	76
Sector federations/consortia	113	74	3	8	4
SUM or percentage	340	174	41	100%	—

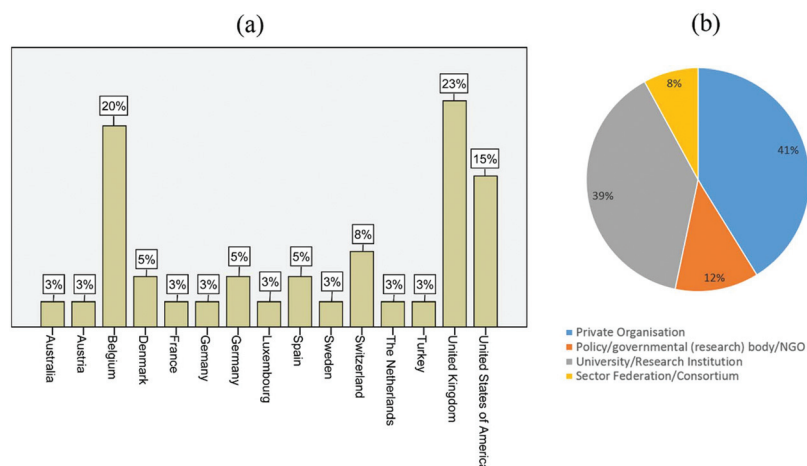


Fig. 3 (a) Geographical spread of the responses. The United Kingdom, Belgium and the United States of America pop out. The authors were able to link a high R&D activity with a high sustainability and compliance awareness; (b) aggregated percentual response rate per stakeholder group.

took part in the survey. Analysing the geographical distribution of the participating parties the United Kingdom, Belgium and the United States of America pop out (Fig. 3a). The rather high participation rate of these countries can be linked with the presence of working groups/organisations like ACS and its Pharmaceutical Roundtable in the USA and RSC and the NHS SDU CSPM in the UK. Belgium is the EU's third highest export country of pharmaceuticals (37 billion Euros in 2014) and is one of the leading countries in innovative pharmaceuticals with R&D and manufacturing sites of JNJ, GSK, Pfizer, Baxter, *etc.* Up to 40% of total revenue is reinjected into innovation investments in R&D. The authors were able to link a high R&D activity with a high sustainability and compliance awareness.^{2,12} At the time of patent loss, generics are eager to take over the market unless the brand company develops a so-called second generation medicine which can be approved if there are significant improvements in patient compliance, efficacy, resource efficiency, sustainability, *etc.* Once approved by the FDA/EMA, a second patent can protect the market of the generics producers. On the other hand, once generics are in the market, it seems that R&D intensive, innovative medicine producers try to make the difference with *e.g.* a more comfortable coating, a higher patient compliance and a better sustainability profile in order to remain competitive in the market.

Zooming in on the structure of the survey, three main topics were questioned: (1) scoping and applications of LCA; (2) data (un)availability and Life Cycle Inventory (LCI) modelling and (3) Life Cycle Impact Assessment Methods (LCIAM) and reaching consensus. The next paragraphs elaborate on the output generated by the stakeholder survey, subdivided in the three aforementioned thematic fields.

Scoping and applications of LCA

More than 75% of all respondents use LCA for hotspot determination to identify the biggest burdens through the Supply Chain (SC). The aforementioned most popular application is

followed by product optimisation and retrofitting (61%). Other stakeholders in the healthcare sector use LCA for sustainability reporting (59%), product development (44%), B2B communications (34%) and Business to Consumers (B2C) communications (24%). Remarkable is that the outreach of results to the wider society (outside of sector federations or bilateral B2B efforts) is rather low (24%) and is the lowest ranked application. While in other sectors LCA or in general environmental sustainability assessment is used in dissemination and marketing materials, the pharmaceutical and healthcare industry is a rather closed community. However, this is gradually changing and this is a definite need to circumvent data unavailability, to improve data transparency and reliability, *etc.* As was already touched upon in the Results and discussion section from the expert interviews, the participants generally do not believe in a product category for pharmaceuticals. 71% of them prefer a product-specific approach over a product group approach whereas a very large range in all impact categories exists due to a very diverse synthesis of APIs, biotechnological drugs, dosing forms, *etc.* This product-specific mind-set is confirmed with the fact that 41% of all applicants use streamlined LCA (less detailed but with specific parameters). 37% of the practitioners use full-blown LCA while for 39% the choice between streamlined and full-blown LCA is inherently connected with the type of application (multiple choice question). Interesting is that of all practitioners using full-blown LCA, 73% use a cradle-to-gate (CtG) approach, 34% a cradle-to-cradle (CtC) approach and 27% a gate-to-gate (GtG) approach (multiple choice). It is commented that the combination of GtG, CtG and CtC is most useful in identifying hotspots and eliminate burdens through the value chain. Next, the terminology 'cradle-to-cradle' seems to be misleading for quite some practitioners (34%). If any, there is very little re-use in the healthcare sector (especially not in the case of pharmaceuticals). The answers for CtC should in fact be Cradle-to-Grave. Even in that case, in reality there are very little studies available on the fate and exposure factors for the derivation of

characterisation factors for End-of-Life (EoL) scenarios in the field of 'pharmaceuticals in the environment'. Some studies were performed deriving characterisation factors for EoL scenarios of API excretion, however this has not been done for metabolites so far.⁵² Probably the most lively topic related to the goal and scope of an LCA is the applied Functional Unit (FU).¹²⁷ Currently, it is common to encounter straight mass FUs such as 'kg', 'mole' or a 'batch' for pharmaceutical products and a 'unit' for medical devices, delivery devices, *etc.* Fair comparisons between products and services are only possible if the FUs are actually comparable.¹²⁸ 76% of all participants acknowledge that there is a need to expand system boundaries in order to take into account healthcare services related to a certain pharmaceutical product (*e.g.* physician visits, hospitalisation, pharmacy, *etc.*) and likewise a shift in FUs from physical attributes (*e.g.* 'kg API', '1 tablet') to the service or treatment offered to the patient (*e.g.* 1 year of treatment). Of course for comparability reasons, this '1 year of treatment' should have the same therapeutic effect as the alternative; a comparison that is hard to make, even with a very multidisciplinary research team. That is probably why 17% are not convinced of this shift and another 7% has no clear opinion.

Life cycle data inventory

As has been touched upon in the section dealing with data (un)availability through the value chain and the visions from the expert panel, primary Life Cycle Data (LCD) for inventory building and transparency within data systems remain to be considered as a key issue. As a main source of primary data inventory, the respondents ranked the specified entries as follows: (1) Bill of Materials (BOM), 56%; (2) Batch Production Reports (BPRs), 49%; (3) Material Safety Data Sheets (MSDS), 44%; (4) equipment manuals, 41%; (5) validations/qualification reports (QA/QC), 37%; (6) Piping and Instrumentation Diagrams (P&IDs), 32%. When the authors questioned the participants on what is to be perceived as the biggest hurdle in LCA overall, confidentiality in data sharing and the lack of both primary and secondary LCD covered more than 60% of all responses. The lack of integration of process design tools and LCA tools, insufficient B2B communication to obtain primary data from suppliers and a lack of harmonisation on how to gather secondary LCD covered the remaining 40%. It is clear that in order to give recommendations for the latter 40%, the issues in confidentiality in data sharing and the lack of secondary LCD need to be tackled. As officially launched on the 6th of February 2014 by the Director General of the DG JRC, and the Deputy Director General of the DG ENV, the European Framework offers the Life Cycle Data Network (LCDN). This network allows for flexibility while facilitating the availability of coherent and quality assured secondary LCD from different organisations and sources.^{129,130} While it was clear from the expert interviews that data sharing within the pharmaceutical sector is still a very sensitive topic, 85% of the participants is convinced of the fact that the lack of secondary LCD on chemical building blocks, solvents, intermediates,

APIs, *etc.* is a crucial aspect that should be tackled. 83% of all participants agree that the establishment of a 'Healthcare Node' or 'Pharmaceuticals Node' in the LCDN or a similar system at a sector federation level – with respect for the IP and competitiveness of data providers – would be a preferred solution to overcome the issue of data unavailability.

Harmonisation and life cycle impact assessment

As the harmonisation of Life Cycle Inventories (LCIs) is being improved by the creation and sharing of secondary LCD through the proposed network in the previous section, Life Cycle Impact Assessment (LCIA) approaches are still very diverse. Looking at midpoint categories, 83% of the participants usually accounts for climate change through the IPCC Carbon Footprint (CF), 59% accounts for water consumption, 46% for fossil resource consumption and about 46% for human toxicity. Fossil resource consumption has been proven to be correlated with climate change indicators such as the IPCC CF.^{53,131,132} Water consumption and human toxicity proved to be relevant impact categories in expressing the environmental impact of pharmaceutical production processes (additionally in relation to the human health benefits).⁴⁶ 56% of the healthcare LCA practitioners never use endpoint indicators related to the three Areas of Protection (AoP). Human health, natural resources and ecosystem species is being accounted for by 39, 29 and 24% of the questioned stakeholders respectively. The lack of harmonisation in the choice of LCIA methodologies to serve different goals and different markets is a key aspect that should be tackled, according to 73% of the survey participants. 66% stated that the European Commission's Product Environmental Footprint (PEF) guideline could be a solid base for harmonisation.

Roundtable discussions

In order to initiate communication, knowledge and data sharing and feeding into discussion groups within the sector, starting the debate on current methodological practices and constraints, the authors organised a two days seminar with presentations and roundtable discussions. The final aim of the seminar was to exchange ideas between different stakeholders (public, private and policy) and to consolidate general recommendations for the sector, taking into account the feedback from the expert interviews and the stakeholder survey. The seminar was organised in Q4 of 2015. Several private organisations (Johnson and Johnson, GlaxoSmithKline, Pfizer, Novartis, Boehringer-Ingelheim, *etc.*) active in the pharmaceutical and more general in the healthcare sector with a broad range of experiences with sustainability assessments, the European Sector Federation EFPIA, the United Nations Development Program on Sustainable Procurement in the Health Sector (UNDP SPHS) and the Sustainable Development Unit of the UK's National Health Service (NHS SDU) were invited to the European Commission's Joint Research Centre in Ispra, Italy, where several crosscutting JRC Units joined the seminar. It was organised by the Institute of Environmental

Sustainability, Sustainability Assessment Unit (IES SA) and Ghent University.

During the first day focus was on dissemination and match-making with presentations from the European Commission of the Life Cycle Data Network (LCDN) and the Product and Organisational Environmental Footprint (PEF & OEF) and introductory presentations from the invited parties. The second day, several roundtable discussions were held on key topics that aroused during day one, the expert interviews and the stakeholder survey with the aim of formulating recommendations for the sector to further advance sustainability assessments in the field.

A second meeting was held on the occasion of a periodic meeting between the members of the Coalition on Sustainable Pharma and Medical Devices (CSPM) of the UK's NHS SDU in London to further fine-tune and align on potential solutions.

The key recommendations and action points condensed by the authors are the following:

(1) In order to integrate pharmaceutical production in the healthcare pathway and to make comparative LCAs on a patient level, it is highly recommended to integrate the complete healthcare pathway in the system boundaries of a certain treatment, not only the pharmaceutical product.¹²⁴ Assessing full healthcare pathways allows for identifying burdens within holistic system boundaries (*e.g.* HVAC at hospitals, medical devices, safety and drug delivery devices, diagnostic devices, *etc.*) and allows for comparison with treatment benefits in terms of health gains (Quality Adjusted Life Years, QALYs). In the end, this is what the sector is delivering to clients; human health is the value. Especially related to current developments towards personalised medicines, this becomes increasingly important.

(2) The establishment of a 'Node' in the LCDN or a similar data system is a highly recommended step to eliminate data gaps, to further expand our knowledge on the sustainability of healthcare processes. The sector prefers this Node to be operational at the level of the (European) sector federations such as the EFPIA. Another potential Node owner could be the UNDP SPHS, the American Chemical Society (ACS), *etc.* The use of black box modelling or the use of so-called system processes in LCI modelling verified by third parties is recommended to safeguard the Intellectual Property (IP) and competitiveness of industrial actors. This should by no means affect the data quality that is delivered to the Node.

(3) More and more organisations are testing how to extract primary data sources from Enterprise Resource Planning (ERP) systems. Primary data sources are still preferred over secondary LCD. Several publications highlight the plausibility and potential success of connecting engineering modelling software (*e.g.* ASPEN) with LCA software or discuss the feasibility of incorporating LCA calculations directly into ERP systems to work with primary data as a fast screening approximation compared to a complete LCI.^{125,133} The authors strongly stimulate further development in merging the aforementioned fields.

(4) There is a clear understanding that there is a lack of harmonisation of impact assessment methodologies in *e.g.* the

UK's NHS Carbon Footprint Guidance,¹³⁴ the International Reference Life Cycle Data System (ILCD) Handbook,^{135,136} the guidelines from the World Business Council on Sustainable Development (WBCSD),¹³⁷ *etc.* There is a clear need to harmonise further development instead of making solutions even more diffuse for different stakeholders. The European Commission's Product Environmental Footprint (PEF) Guidelines¹³⁸ might be a good alternative, following on the ILCD Handbook. However, at this stage, the PEF and Organisation Environmental Footprint (OEF) at the corporate level are still in the pilot testing phase. The pharmaceutical sector is not subject of any of those pilots, but should be able to grasp learning (pros and cons) from the chemical and consumer products' pilots. In future, it should be evaluated to what extent the PEF and OEF can help harmonisation in the pharmaceutical and healthcare sector.

Methodology

Literature review

A thorough literature review was performed of which a condensed version is presented in the Results and discussion section. For this, the Web of Science™ from Thomson Reuters™ was used. As a time window, publications ranging from January 1997 to April 2016 were considered. Table 1 lists a complete, chronological list of relevant research papers. The detailed version including authors, publication year, years published, publication type, topic, Impact Assessment Method (IAM), applied system boundaries, citations, citations per year, journal (ISO abbreviations), journal ranking through Impact Factor (IF) and research field quartile is made available in ESI 1.† The search criteria are predefined topics related to sustainability assessment, Life Cycle Assessment (LCA), resource footprinting, carbon footprinting and Green Chemistry (GC) metrics in the pharmaceutical and healthcare sector. In the first stage, 125 articles were found over the different categories. Upon abstract reading, unrelated articles and double counted articles over the predefined categories were eliminated. 101 peer reviewed scientific articles were retained in the literature review. The extended list of the literature can be found in ESI 1,† together with all categories (*e.g.* types of publications: case study, review, methodological framework, perspective, *etc.*). Six of the most cutting-edge and most cited articles as milestones within the field of sustainability assessments on pharmaceuticals and the healthcare sector were selected to be discussed in the Results and discussion section of this paper. Fig. 4 illustrates the reasoning for the selected articles within the category of Green Chemistry (GC) related to pharmaceutical production. Fig. 4a shows for all categories that the Impact Factor (IF) per year is all but correlated with the amount of citations per year of certain articles. In Fig. 4b, it becomes clear that the highest citations are obtained through the type of article: perspective or review article with recommendations, rather than with publishing in a journal with a high IF. In the field of GC, three of the most cited papers within the IF range between 2.5

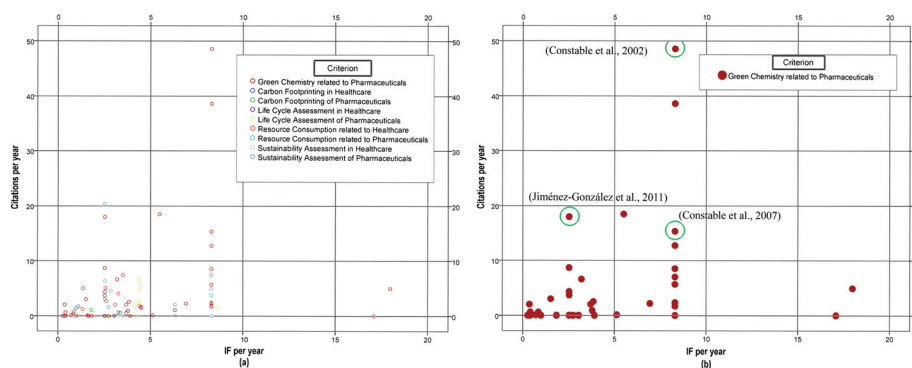


Fig. 4 (a) Shows for all categories that the Impact Factor (IF) per year is all but correlated with the amount of citations per year of certain articles. In (b), it becomes clear that the highest citations are obtained through the type of article: perspective or review article with recommendations, rather than with publishing in journals with a high IF. In the field of Green Chemistry, three of the most cited papers within the IF range between 2.5 and 8.3 were selected, all of them being comprehensive reviews or perspective articles with recommendations.

and 8.3 were selected, all of them being comprehensive reviews or perspective articles with recommendations.

Expert interviews

The authors approached 13 field experts with experienced functions ranging from sustainability directors in industry, product stewardship directors, LCA project managers, executive managers, academic professors and so forth. Out of the 13 invitations, 8 expert interviews were conducted, resulting in a response rate of 62%. To protect the privacy of the experts at hand and of their legal entities, the sections in Results and discussion are reflecting on the discussions and visions within the group. They shall not represent any statements of either the individual or its affiliations. With respect to the expert interviews, 3 private drug producing companies were questioned, 2 non-profit corporations governed by a single Board of Directors, 2 private sustainability consulting companies and 1 academic entity.

Stakeholder survey

Concerning the stakeholder survey, the authors invited (1) private organisations; (2) policy, governmental (research) bodies & NGOs; (3) university/research institutions; (4) sector federations/consortia and (5) consumers (hospitals, pharmacies, patient organisations, and physicians). As previously presented in the Results and discussion section, 344 potential participants were invited over the different stakeholder subcategories. They were selected based on their track record, proven relevance to the scope of this research, corporate sustainability reports, *etc.* However, several people conducting different roles within one legal entity were approached while almost every entity has sent in an aggregated entity vision or response. Unfortunately, we did not receive any response from the consumer category, despite three reminders. As a result, this category was left out of consideration, ending up with a total of 340 invitees. Of these 340, 174 were unique identifiers, yielding a response rate of 24% (41 responses). Table 2 provides more details about invitations, unique identifiers and

responses. Fig. 2 gives an overview on the aggregation ratio per stakeholder group, as was explained in the Results and discussion section.

Roundtable discussions

As touched upon in the Results and discussion section, the roundtable discussions were organised in Q4 of 2015 by the JRC's Institute of Environmental Sustainability, Sustainability Assessment Unit (IES SA) and Ghent University. Several private organisations active in the pharmaceutical and more general in the healthcare sector with a broad range of experiences with sustainability assessments, the European Sector Federation EFPIA, the United Nations Development Program on Sustainable Procurement in the Health Sector (UNDP SPHS) and the Sustainable Development Unit of the UK's National Health Service (NHS SDU) were invited to the European Commission's Joint Research Centre in Ispra, Italy, where several crosscutting units of different JRC Institutes joined the seminar. The final aim of the seminar was to discuss and report on recommendations for the sector to further advance sustainability assessments in the field.

Conclusions and outlook

This perspective paper is the result of the work of many participant groups and devoted individuals to take sustainability assessments of pharmaceuticals products or services within the healthcare sector to the next level. Through literature reviews, expert interviews, stakeholder surveys and roundtable discussions, the authors triggered a dialogue in the community resulting in a prioritisation of bottlenecks in conducting environmental sustainability assessments of pharmaceutical products and services within the healthcare sector. Next, recommendations and key actions are suggested in order to overcome the aforementioned hurdles. The most challenging bottleneck proved to be the lack of primary process data in order to build life cycle inventories and the lack of secondary data

within life cycle databases. To tackle the first priority, a preferred list of targeted documents was given by practitioners to extract primary data from. Next, the authors highlighted new developments in coupling Enterprise Resource Planning (ERP) systems with life cycle metrics and *vice versa*. With respect to the second priority 83% of all survey participants agreed that the establishment of a 'Healthcare Node' or 'Pharmaceuticals Node' in the EU Life Cycle Data Network (LCDN) or a similar system at a sector federation level – with respect for the IPR and competitiveness of data providers – would be a preferred solution to overcome the issue of data unavailability. The authors strongly suggest and will keep on facilitating roundtable discussions and debates (*e.g.* at EFPIA, NHS SDU, *etc.*). Next, the authors urge to make use of existing platforms from the European Commission and UNEP or others to streamline data inventories. More stakeholders (especially patient populations) should be convinced to take part in the debate. It is a strong belief of the authors and all stakeholders involved that this paper should be used as guidance to steer further research and development in industry, academia and policy in order to serve and support decision making processes.

Abbreviations

ACS	American Chemical Society
ACS GCI	American chemical Society Green Chemistry Institute
ACS GCIFR	American Chemical Society Green Chemistry Institute Formulators Roundtable
ACS GCIPR	American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable
AE	Atom efficiency
AMI	Aqueous mass intensity
AoP	Area of protection
API	Active pharmaceutical ingredient
B2B	Business to business
B2C	Business to consumers
BPR	Batch production report
BOM	Bill of materials
BSI	British Standards Institution
CF	Carbon footprint
CSPM	Coalition on Sustainable Pharmaceuticals and Medical Devices
CtC	Cradle-to-cradle
CtG	Cradle-to-gate
DALY	Disability adjusted life year
DG	Directorate-General
DtV	Design to value
EC	European Commission
ECHI	European Core Health Indicators
EFPIA	European Federation of Pharmaceutical Industries and Associations
EIT	European Institute for Innovation and Technology

ELCD	European Life Cycle Database
EMA	European Medicines Agency
EoL	End-of-life
ERM	Environmental resource management
ERP	Enterprise resource planning
ERs	Execution requirements
EU	European Union
FDA	Food and Drug Administration
FLASC	Fast life cycle assessment of synthetic chemistry
FU	Functional unit
GC	Green chemistry
GCM	Green chemistry metrics
GDP	Gross domestic product
GHG	Greenhouse gas
GP	General practitioner
GSK	GlaxoSmithKline
GtG	Gate-to-gate
GWP	Global warming potential
IAM	Impact assessment method
IES	Institute for Environmental Sustainability
IF	Impact factor
ILCD	International Reference Life Cycle Data System
IP	Intellectual property
IPCC	Intergovernmental Panel on Climate Change
IPR	Intellectual property rights
ISO	International Organization for Standardization
JNJ	Johnson and Johnson
JRC	Joint Research Centre
KIC	Knowledge and Innovation Community
KIC RM	Knowledge and Innovation Community on Raw Materials
LC	Life cycle
LCA	Life cycle assessment
LCC	Life cycle costing
LCD	Life cycle data
LCDN	Life cycle data network
LCI	Life cycle inventory
LCIA	Life cycle impact assessment
LCIAM	Life cycle impact assessment method
LCM	Life cycle management
LM	Large molecules
MCDM	Multi-criteria decision making
MSDS	Materials safety data sheet
NGO	Non-governmental organisation
OEF	Organisational environmental footprint
P&ID	Piping and instrumentation diagram
PAS	Publicly available specification
PEF	Product environmental footprint
PMI	Process mass intensity
QA	Quality assurance
QbD	Quality by design
QC	Quality control
R&D	Research and development
RME	Reaction mass efficiency
SA	Strategic agenda

SC	Supply chain
SM	Small molecules
TRL	Technology readiness level
UK	United Kingdom
UK NHS	United Kingdom National Health Service
UK NHS SDU	United Kingdom National Health Service Sustainable Development Unit
UNEP	United Nations Environmental Program
UNDP	United Nations Development Program
UNDP SPHS	United Nations Development Program on Sustainable Procurement in the Health Sector
US	United States
VC	Value chain
WBC	World Business Council
WBCSD	World Business Council on Sustainable Development

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