In pursuit of our dreams of a healthy future where people mean no harm

"Er ist ein Denker: das heißt, er versteht sich darauf, die Dinge einfacher zu nehmen, als sie sind."

"Fröhlichen Wissenschaft", 1882

- Friedrich Wilhelm Nietzsche -

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	Vakgroep Duurzame Organische Chemie en Technologie
Copromotor	Bert Heirman
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UNIVERSITEIT
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Faculty of Bioscience Engineering

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Advancing Environmental Sustainability Assessment in the Pharmaceutical Industry

Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in Applied Biosciences

2016

Dutch translation of the title:
Geavanceerde Milieuduurzaamheidsbeoordeling in de Farmaceutische Industrie

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A word of thanks

What once seemed all but obvious happened four years ago: I started a PhD in bioscience engineering. Fascinated by sustainability in pharmaceutical sciences, I was blessed to work out my own proposal within a framework of a strong collaboration with Janssen Pharmaceutica, Johnson and Johnson. Building on the work of my predecessor Geert Van der Vorst, I got the chance to continue research towards environmental sustainability in close interaction with industry thanks to my promotors Prof. Jo Dewulf and Bert Heirman, Sr. Principal Product Stewardship Compliance and EU Packaging.

Jo, you triggered me with a challenging master thesis in the same field to keep on working on difficult bottlenecks in the form of a PhD study instead of going into industry. I enjoyed working in a mixed academic-industrial environment. Thank you, Jo, for your guidance, even more for sharing your experience and advice especially when one has to make choices and priorities. You manage to let junior researchers operate with a lot of freedom developing themselves and adjust the steering wheel whenever necessary.

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A word of thanks

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One does not commit to a PhD study of four years without a pleasant and motivating working environment (at least, that is what you hope for). I had the pleasure to be surrounded by an enthusiastic team of colleagues, being at Ghent University, Janssen or the European Commission in Italy. Thank you, my friends of EnVOC, in particular Jo, Steven, Xander, Sam, Gaby, Sue Ellen, Sophie x 2, all my thesis students, and too many other people to acknowledge here. Thank you to many people at the Janssen Group, in particular Bert, Bart, Phil, Philippe, Jack and a list of two pages of colleagues that helped me while analysing production plants in Beerse, Geel, Olen, Leiden, Shaffhausen and Latina. Last but not least, thank you to my fellow JRC trainees of 2015 for the joyful moments we shared.

I guess what a word of thanks is all about is a humble 'thank you' to those who shared pain and glory along the way. Choosing for a PhD as for an MBA is choosing for a lifestyle with very intensive periods. It is a choice that affects your closest surroundings. To all my friends, in particular my two closest friends Thomas and Fabian, a well-deserved 'thank you', to help me carry that burden. I cannot promise I will not be at your doorstep anymore now this work is finished. Ah well, just admit you enjoyed the talks as well!

My family, parents, parents in law, thank you for supporting me, for always believing in me and helping me until the very last day of my PhD. The support I had from you means the world to me. And as we know, world's resources are getting scarce. It is something to hold on to.

Behind every great sportsman, there is an even greater woman. Behind every great politician, there is an even greater person. I would not say I was a great PhD student, but I did something with devotion, and to do so, to keep on believing in your case, you need a great person on your side. You literally nursed me during the last months of this journey. Well, months… You took care of me since the moment we met, we married, we started building our lives and persecuting our dreams. Together, we are strong, entrepreneurial, ambitious and – above all – complementary supportive. Sara, 'thank you' is a non-proportional way of expressing my gratitude for your unconditional love and support. I owe you.

Wouter De Soete, December 2016, Brakel

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The author wants to acknowledge Janssen Pharmaceutica NV, Janssen Biologics and Janssen-Cilag SpA of the Janssen Group (Johnson & Johnson Family of Companies) for their support and transparency in a very time consuming data inventory. Several teams were mobilised to help collecting data from the data management systems. Special thanks go to the teams in the production facilities of Geel and Beerse (Belgium), Leiden (The Netherlands), Latina (Italy), Schaffhausen (Switzerland) and Cork (Ireland). This acknowledgement holds for almost every chapter in this PhD dissertation.

Related to Chapter 2 and Chapter 6, the author had the privilege of leading a project on Sustainability in the Pharmaceutical and Healthcare sector at the Joint Research Centre of the European Commission in Italy. Many thanks go to the support of the Sustainability Assessment team (H.08) of the Institute for Environmental Sustainability for their support and hospitality. It cannot be stressed enough how important the stakeholder contribution of the sector was to this research. Therefore, the author wants to thank every individual and organisational entity that has contributed in one way or another to these research chapters. Acknowledgements are granted to all stakeholders cooperating in the survey, expert interviews and roundtable discussions, with in

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Related to Chapter 4 data on the continuous production line ConsiGma™ were obtained from GEA Pharma Systems NV - Collette™. By conducting this study, the author was awarded with the Solvay Sustainable Chemistry Award 2012. A word of thanks should be given to the Solvay International Chemical Group for endorsing the innovative character and industrial relevance of this research.

Focusing on Chapter 5, two years of intensive research crossed company borders and was performed with a diverse, multidisciplinary team. The authors would like to acknowledge the complete team of Johnson & Johnson and Baxter Healthcare working on data inventory in all production stages. The resource accounting and the assessment in general was performed by a team of LCA professionals of Ghent University and Thinkstep International (former PE International) and coordinated by the PhD candidate. This project was partly funded by the Consejo Nacional de Ciencia y Tecnología (CONACYT), Mexico (Grant Number 216175).

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Summary/Abstract

This PhD dissertation comprises generally four main parts, subdivided in 10 chapters. A first part will guide the reader through a series of principles and methodologies related to (environmental) sustainability and its evolution in time within processing industries. Next, environmental sustainability is applied to the pharmaceutical sector. The economic relevance of this Added Value manufacturing industry is clearly illustrated according to various sources such as the R&D investment scoreboard of the European Commission (up to 40% of all revenue is reinvested in R&D applications). This while R&D intensity can be linked with the willingness to include environmental performance in prospective technologies and new compounds.

A second part deals with some very specific and timely technological improvement strategies in pharmaceutical manufacturing and the environmental performance of that compared to the alternatives through resource based Life Cycle Assessment. Potentially the breakthrough of this decade is continuous manufacturing in pharmaceutical manufacturing. In case of the continuous wet granulation (ConsiGma) compared to batch processing one does not only reduce lead times, enables pull production, one also reduces the cumulative natural resource footprint with 34.0%. Another very lively and fast moving field in providing medicines is the introduction of the so-called Large Molecules or biologicals. The conventional very fossil intensive chemistry needed to produce a pharmaceutical compound consumes up to 70 to 80% of fossil resources (in relative terms of the total resource footprint). The author investigated the difference in resource extraction patterns between these so-called Small Molecules and biologicals (starting from a biologic feedstock such as animal cells or virus

strains). In relative contributions, it was proven that the production of biologics is almost as fossil intensive as the production of Small Molecules, in contrast to what was expected. This is mainly due to the long fermentation processes and the use of buffer media for downstream separation techniques of the proteins. While on a compound basis the production of biologicals proved to be about 4 times more resource intensive, on a yearly treatment basis though, the opposite was found. Due to the very unique characteristics of the monoclonal antibodies (proteins) as long acting platforms, Small Molecules scored about 250 times worse than biologicals, revealing the need for system expansion from compound level to the complete healthcare pathway.

Part three of this dissertation constructs a set of methodologies that can be used by businesses to enhance the value of Life Cycle Assessment within the organisation. Part three focusses primarily on:

(1) Revealing the needs, bottlenecks and upcoming challenges in order to advance the state of the art. This work was done at the Joint Research Centre of the European Commission including more than 300 stakeholders. The main outcomes were to be found in the field of Life Cycle Inventory modelling and goal and scope definition (system expansion, functionalities, etc.). Some of these identified bottlenecks are dealt with in the next chapters of part three.

(2) The derivation of technology experience curves (in this dissertation for Wet Granulation) in order to include environmental performance indicators in early R&D decision trees. This enables a proactive way of dealing with environmental sustainability in Quality by Design.

(3) The establishment of a set of forecasting equations with 1-5 readily available predictor variables as a streamlined Life Cycle Assessment method to calculate the cumulative resource consumption of Active Pharmaceutical Ingredients in full scale production.

(4) *A framework on how integration of resource based environmental sustainability assessment can be implemented in operational management systems within businesses.*

To end with, part four provides in chapter 10 overall conclusions of this dissertation together with an outlook on (1) implementation of the methodologies developed in this work and (2) future methodological challenges to be addressed on the micro level, macro level and within the multidisciplinary fields of coupling Operational Excellence and resource based Life Cycle Assessment.

Samenvatting/Abstract

Dit doctoraat bestaat hoofdzakelijk uit 4 delen, onderverdeeld in 10 hoofdstukken. Een eerste deel geeft een aanzet voor de lezer over (milieu)duurzaamheid, methodologieën om (milieu)duurzaamheid in kaart te brengen en de evolutie ervan in de maakindustrie. Het tweede hoofdstuk van deel één geeft een toegepaste benadering van grondstoffen-gebaseerde (milieu)duurzaamheid in de farmaceutische sector. De economische relevantie van de waardecreatie in deze sector is van onmiskenbaar belang, zo blijkt o.a. uit het 'R&D Scoreboard' van de Europese Commissie. Tot 40% van de totale omzet in de sector wordt opnieuw geïnjecteerd in innovatiegerichte R&D-toepassingen. Daarnaast is er een duidelijke link tussen R&D-intensiteit in de maakindustrie (meer specifiek de farmaceutische industrie) en de toepassing van grondstoffen-gebaseerde (milieu)duurzaamheids-indicatoren in beslissingsbomen in de ontwikkeling van nieuwe technologieën en actieve farmaceutische stoffen.

Deel twee behandelt een aantal zeer specifieke en actuele technologische ontwikkelingen die de jongste jaren hun implementatie kennen (of zullen kennen) in de farmaceutische industrie. Wellicht is de meest belangrijke doorbraak van dit decennium de introductie van continue productietechnologieën (flow productie) die geoptimaliseerd werden ter implementatie in de farmaceutische industrie. In het geval van tablettering aan de hand van natte granulatie en directe compressie bewijst de continue productietechnologie (ConsiGma) een reductie van de grondstoffenvoetafdruk van 34.0%. Een ander zeer actief en innovatief domein is dat van de zogenaamde biologische medicijnen (niet te verwarren met homeopathische producten). Biologische medicijnen kennen evenzeer een industriële

productieroute maar de primaire grondstof is biologisch van aard (bv. dierlijke cellen, DNA-materiaal van virussen, etc.). Terwijl bij de conventionele chemische synthese typisch 70-80% van de grondstoffenvoetafdruk te wijten is aan het gebruik van fossiele grondstoffen doorheen de verschillende fasen van de levenscyclus werd verwacht dat voor biologische geneesmiddelen de voetafdruk bepaald zou worden door landgebruik, biomassa en water. Niets blijkt echter minder waar. Niettegenstaande de biologische aard van de celcultuur blijft het maken van biologische medicijnen een energie-intensief proces, in dit geval door fermentatie en het gebruik van bufferoplossingen tijdens de opzuivering van de proteïnen. De relatieve contributie tot de voetafdruk verandert slechts in heel beperkte mate t.o.v. chemische synthese. Wel blijkt dat op product-niveau ongeveer 4 keer zoveel grondstoffen nodig zijn in de productie van biologische medicijnen versus chemisch gesynthetiseerde. Op een jaarlijkse behandelingsbasis echter blijkt net het omgekeerde: ongeveer 250 keer meer grondstoffen zijn vereist in de productie van chemisch gesynthetiseerde medicijnen omwille van de typische karakteristieken van monoklonale antilichamen als biologische proteïnen, namelijk hun 'long acting' platform. Uit deze vaststelling blijkt duidelijk dat men binnen levenscyclusanalyse een herziening (uitbreiding) dient te doen van de systeemgrenzen om de juiste functionaliteiten te behelzen die effectief waarde bevatten.

Het derde luik van deze thesis brengt een set methodologieën samen die gebruikt kunnen worden door bedrijven/organisaties om de waarde van grondstoffen-gebaseerde levenscyclusanalyse optimaal te valoriseren. Deel drie focust hoofdzakelijk op:

(1) De identificatie van de noden, tekortkomingen en toekomstige uitdagingen binnen de nieuwste ontwikkelingen met als doel grensverleggend tot deze laatste bij te dragen. Deze studie is uitgevoerd aan het Joint Research Centre van de Europese Commissie te Ispra (Italië) van waaruit meer dan 300 stakeholders betrokken werden. De belangrijkste bevindingen positioneerden zich in het domein van levenscyclus inventory modellering en het bepalen van de scope van de studie (systeemexpansie, functionaliteiten, enz.). Aan een aantal van deze tekortkomingen worden in de volgende hoofdstukken potentiële oplossingen geboden.

(2) *De constructie van 'technology experience curves' (in dit geval voor de natte granulatie technologie). Dit stelt ons in staat om in een vroeg onderzoeksstation reeds milieuperformantie-indicatoren te integreren in R&D-beslissingsbomen om op die manier te anticiperen op de milieu-impact die op grote 'manufacturing' schaal zou teweeg gebracht worden.*

(3) *De berekening van een set predictievergelijkingen met 1 – 5 predictievariabelen met als doel een 'streamlined' levenscyclusanalyse mogelijk te maken om de cumulatieve grondstoffenvraag van farmaceutisch actieve componenten eenvoudig in kaart te brengen.*

(4) *Een framework ter integratie van grondstoffen-gebaseerde levenscyclusanalyse in bestaande datasystemen binnen operationeel management in bedrijfsomgevingen.*

Als slot biedt deel vier een aantal overkoepelende conclusies van dit doctoraatsonderzoek samen met perspectieven voor verder onderzoek gerelateerd aan: (1) implementatie en valorisatie van de methodologieën ontwikkeld binnen dit onderzoek en (2) toekomstige methodologische uitdagingen en opportuniteiten op microschaal (bedrijfsniveau) en macro-economisch niveau en ten slotte de hybridisatie van multidisciplinaire analysemethoden binnen Operational Excellence en grondstoffen-gebaseerde levenscyclusanalyse.

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List of 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
AR4	Fourth Assessment Report
AR5	Fifth Assessment Report
AVM	Added Value Manufacturing
BA	Business Administration
B2B	Business to Business
B2C	Business to Consumers
BMS	Bristol-Myers Squibb
BPR	Batch Production Report
BO	Basic Operation
BOM	Bill of Materials
BCS	Biopharmaceutics Classification System
BSI	British Standards Institution
CE	Circular Economy

CEENE	Cumulative Exergy Extracted from the Natural Environment
CExD	Cumulative Exergy Demand
CF	Carbon Footprint
CI	Confidence Interval
CIP	Cleaning in Place
C/O	Changeover
COD	Chemical Oxygen Demand
COP	Coefficient of Performance
CP	Cleaner Production
CSPM	Coalition on Sustainable Pharmaceuticals and Medical Devices
CSR	Corporate Sustainability Reporting
CT	Clean Technology
CtC	Cradle-to-Cradle
CtG	Cradle-to-Gate
DA	Digital Agenda
DALY	Disability Adjusted Life Year
DC	Direct Compression
DDD	Defined Daily Dose
DDP	Delivery Device Production
DF	Dosage Form
DfE	Design for Environment
DG	Directorate-General
DG ENV	Directorate-General for Environment
DG JRC	Directorate-General Joint Research Centre
DP	Drug Product
DPC	Direct Product Capture
DPP	Drug Product Production
DtV	Design to Value
EA	Exergy Analysis

EC	European Commission
ECHI	European Core Health Indicators
EEIOA	Environmentally Extended Input-Output Analysis
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHS	Environmental Health and Safety
EHS&S	Environmental Health and Safety and Sustainability
EIT	European Institute for Innovation and Technology
EL	Exergy Loss
ELCA	Exergetic Life Cycle Assessment
ELCD	European Life Cycle Database
ELCIA	Exergetic Life Cycle Impact Assessment
EMA	European Medicines Agency
EoL	End-of-Life
EPD	Environmental Product Declaration
ERM	Environmental Resource Management
ERP	Enterprise Resource Planning
EU	European Union
Ex	Exergy
$Exergy_{in}$	Exergetic input of a system
$Exergy_{out}$	Exergetic output of a system
FDA	Food and Drug Administration
FLASC	Fast Life Cycle Assessment of Synthetic Chemistry
FU	Functional Unit
GC	Green Chemistry
GCI	Green Chemistry Initiative
GCIPR	Green Chemistry Initiative Pharmaceutical Roundtable
GCM	Green Chemistry Metrics

GDP	Gross Domestic Product
GHG	Greenhouse Gas
GMP	Good Manufacturing Practice
GP	General Practitioner
GSK	GlaxoSmithKline
GSP	Good Supply Practice
GtG	Gate-to-Gate
GWP	Global Warming Potential
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl methylcellulose
HR	Human Resources
HVAC	Heating, Ventilation and Air Conditioning
IAM	Impact Assessment Method
ICT	Information and Communication Technology
IE	Industrial Ecology
IES	Institute for Environmental Sustainability
IES SA	Institute for Environmental Sustainability, Sustainability Assessment Unit
IF	Impact Factor
ILCD	International Reference Life Cycle Data System
IOA	Input-Output Assessment
IoT	Internet of Things
IP	Intellectual Property
IPCC	Intergovernmental Panel on Climate Change
IPR	Intellectual Property Rights
ISO	International Organization for Standardization
IT	Information Technology

JIT	Just in Time
JNJ	Johnson & Johnson
JRC	Joint Research Centre
JRC IES SA	Joint Research Centre, Institute of Environmental Sustainability, Sustainability Assessment Unit
KIC	Knowledge and Innovation Community
KIC RM	Knowledge and Innovation Community on Raw Materials
KPI	Key Performance Indicators
LAR	long-Acting-Release
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
LCSA	Life Cycle Sustainability Assessment
LCT	Life Cycle Thinking
LHV	Lower Heating Value
LM	Large Molecule
MAB	Monoclonal Antibody
MCDM	Multi-Criteria Decision Making
MCC	Microcrystalline cellulose
ME	Molar Efficiency
MES	Manufacturing Execution System
ML	Machine Learning

MRP	Manufacturing Resource Planning
MSDS	Materials Safety Data Sheet
MW	Molecular Weight
NGO	Non-Governmental Organisation
NHS	National Health Service
NHS SDU	National Health Service Sustainable Development Unit
NIR	Near Infrared Spectroscopy
NVA	Non Value Adding
OE	Operational Excellence
OECD	Organisation for Economic Cooperation and Development
OEE	Overall Equipment Effectiveness
OEF	Organisational Environmental Footprint
P&ID	Piping and Instrumentation Diagram
PAS	Publicly Available Specification
PCR	Product Category Rule
PDC	Process Development Centre
PE	Polyethylene
PEF	Product Environmental Footprint
PIE	Pharmaceuticals In the Environment
PLC	Programmable Logic Controller
PMI	Process Mass Intensity
PR	Pharmaceutical Roundtable
PROSUITE	PROspective SUstainability assessment of TEchnologies
PRW	Process Reaction Water
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QbD	Quality by Design

QC	Quality Control
R&D	Research and Development
RME	Reaction Mass Efficiency
RSC	Royal Society of Chemistry
SA	Strategic Agenda
SAP	Systems, Applications & Products in Data Processing
SC	Supply Chain
SCADA	Supervisory Control And Data Acquisition
SCM	Supply Chain Management
SDF	Solid Dosage Form
SDU	Sustainable Development Unit
SLCA	Social Life Cycle Assessment
SLCM	Sustainable Life Cycle Management
SM	Small Molecules
SOP	Standard Operating Procedure
SRES	Special Report on Emissions Scenarios
SSCM	Sustainable Supply Chain Management
S/U	Set-up
TAR	Third Assessment Report
ToC	Theory of Constraints
TPS	Toyota Production System
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
UN	United Nations

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
US EPA	United States Environmental Protection Agency
VA	Value Assessment
VC	Value Chain
VSE	Value Stream Engineering
VSM	Value Stream Management
WBC	World Business Council
WBCSD	World Business Council on Sustainable Development
WCED	World Commission on Environment and Development
WG	Wet Granulation
WHO	World Health Organisation
WS	Work Station

List of Symbols

add	Additives
cat	Catalysts
$CEENE_j$	Cumulative Exergy Extracted from the Natural Environment for a product or service j
c_p	Isobaric specific heat capacity
Ex	Total exergy of a material stream
ex_{ch}	Molar chemical exergy
ex_j^{CH}	Molar chemical exergy of substance *j*
$ex^{\circ CH}_j$	Standard molar chemical exergy of substance *j*
$ex^{\circ CH}_{el}$	Standard partial molar chemical exergy of molecules of substance *j*
Ex^{CH}	Chemical exergy of a material stream
Ex^{KN}	Kinetic exergy of a material stream
Ex_{loss}	Exergy loss
ex_{mix}	Molar mixing exergy
Ex^{M}	Mechanical exergy of a material stream
Ex^{PH}	Physical exergy of a material stream
Ex^{PT}	Potential exergy of a material stream
Ex^{T}	Thermal exergy of a material stream
Ex_{sys}	Total exergy of a system
Ex_{sys}^{CH}	Chemical exergy of a system
Ex_{sys}^{KN}	Kinetic exergy of a system
Ex_{sys}^{M}	Mechanical exergy of a system
Ex_{sys}^{PH}	Physical exergy of a system
Ex_{sys}^{PT}	Potential exergy of a system

Ex_{sys}^{T}	Thermal exergy of a system
g	Gravitational acceleration
$\mathrm{Gt_{oe}}$	Equivalent amount of energy released by burning one ton of crude oil
H	Enthalpy of stream
H_0	Enthalpy of reference state
m	Mass of the material stream
n	Number of moles
n_{el}	Number of molecular elements of substance j
n_j	Mole fraction of substance j in the material stream
p	Pressure of system
p_0	Pressure of reference state
Q_{h}	Energy of the heat source
R	Universal gas constant
$solv$	Solvents
sm	Starting molecules
S	Entropy of stream
S_0	Entropy of reference state
S_{gen}	Entropy generated
T	Temperature of a system
T_h	Temperature of the heat source
T_0	Temperature of reference state
U	Total internal energy of a system
U_0	Total internal energy of reference state
V	Volume of a system
V_0	Volume of reference state
$\bar{v}$	Velocity of material stream
X_i	X factor of the i^{th} reference flow
x_i	Molar fraction of compound i
z	Elevation height relative to the reference environment
z_i	Charge of ion i

List of Greek Symbols

α	Process level
a_i	Effective diameter of ion i
a_{ij}	Cumulative amount of the reference flow per Functional Unit
β	Plant level
β	Exergy to energy ratio
γ	Overall industrial level
γ_i	Activity coefficient of compound i
$\Delta_f G^\circ_j$	Standard Gibbs free energy of formation of substance *j*
η_1	Simple efficiency
η_2	Rational efficiency
η_3	Utility efficiency
μ	Chemical potential
μ_0	Chemical potential of the reference flow

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Part 1: Introduction

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Chapter 1
Environmental Sustainability

Partly redrafted from:

De Soete, W., Dewulf, J. et al. (2013). "Exergetic Sustainability Assessment of Batch versus Continuous Wet Granulation based Pharmaceutical Tablet Manufacturing: a Cohesive Analysis at Three Different Levels." Green Chemistry **15**(11): 3039 - 3048.

1.1 Introduction

Probably the very first man to openly question the earth's limits by introducing the concept of sustainability was the German miner Hans Carl von Carlowitz. In his 'Sylvicultura oeconomica' (1713), he stated timber was only meant to be cut in the amount it was regrown, with forestry having to ensure that soil fertility was maintained (García-Serna et al., 2007). It took several ages for mankind to approximately quantify consumption patterns and their consequences on the environment. The American Geophysicist M. King Hubbert (1956) is assumed to be the first scientist who was able to create a method of modelling the consequences of the industrial activity after the second World War. Bearing in mind his assumption that the reserves for all different commodities do not increase, the peak of maximum mineral extraction from the earth would be reached by 2020, exceeding 12 Gt_{oe}/year. Regarding oil though, the maximum consumption would be reached by 2008, leading to a shift in energetic resource consumption from oil and natural gas to coal (Delgado, 2008). In the second half of the 20^{th} century, several alarming publications were made by for instance Rachel Carson. In her 'Silent Spring' (1962), she denounces the environmental problems caused by synthetic pesticides (García-Serna et al., 2007). This work was found to be part of the base to the establishment of the US Environmental Protection Agency (US EPA). Nevertheless, it took until the publication of the Brundtland report 'Our Common future' (1987) to formulate a comprehensive definition of the sustainability concept. Since then, the awareness has been growing in the international scientific community. Sustainable development was often quoted as 'development that meets the needs of the present without compromising the ability of future generations to meet their own needs' (García-Serna et al., 2007). Since world's famous report on 'The Limits to Growth' (1972, Club of Rome), the limitation to resource availability became more and more a

true reason for concern. A shift in attitude of mind from a more prominent point of view on sustainability to a necessity resulted in a worldwide demand for sustainable products and services. Although Meadows and Meadows were not the first to question the earth's physical limits, the report was conceived in a rather sceptical way (Meadows and Meadows, 2007). The report claimed the population to grow in an exponential way, while the ability of technology to increase availability of resources seemed to be a linear process. Aurelio Peccei, founder of the Club of Rome agreed to promote the report as being official in the spring of 1971, despite of the anxious reactions of his fellow colleagues, which would foreshadow the world's reaction (Meadows and Meadows, 2007; Girod et al., 2009). Recent reports on sustainability include the Special Report on Emissions Scenarios (SRES), made by the Intergovernmental Panel on Climate Change (IPCC) in 2000. These SRES scenarios were used to produce the IPCC Third Assessment Report (TAR) (2001) and the IPCC Fourth Assessment Report (AR4), published in 2007. The main outcome of the report was that warming of the climate system would be unequivocal and that it was very likely due to the observed increase in anthropogenic greenhouse gas emissions (Girod et al., 2009). The IPCC Fifth Assessment Report (AR5) focused a lot on uncertainties due to evaluation and assessment methods in the scenario analysis (Mastrandrea et al., 2011). Few of its main projections were further warming with likelihood to exceed 2.0°C for many scenarios, change of global water cycles affecting ecosystems even in the first trophic levels, etc. (Kavvada et al., 2013).

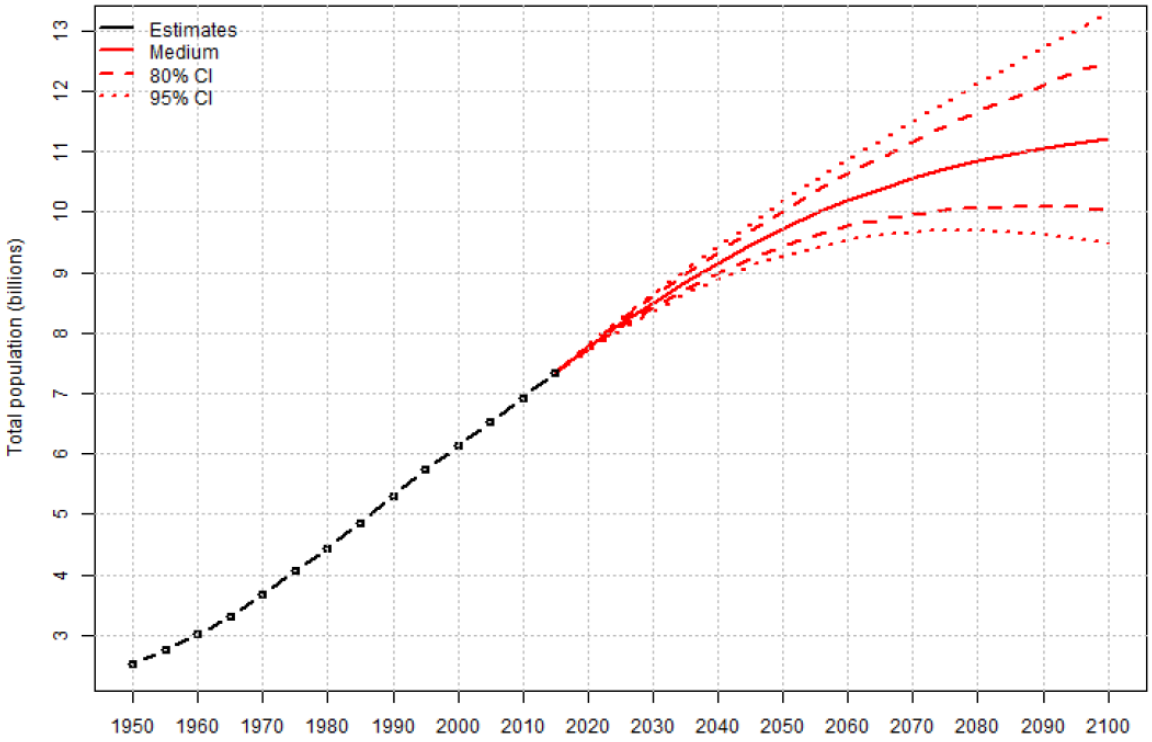

Figure 1: World population: estimates, 1950-2015, medium-variant projection and 80 and 95 per cent confidence intervals, 2015-2100. Adopted by United Nations, 2015.

At the end of the 18th century, the earth's population was only one billion. By the next century, the world's population approached six billion people (Figure 1). In November 2011, human population exceeded seven billion. According to the United Nations (UN), the world population continues to grow more slowly than in the recent past. Today, it is growing by 1.18 (compared to 1.24 ten years ago) per cent per year, or approximately an additional 83 million people annually. The world population is projected to increase by more than one billion people within the next 15 years, reaching 8.5 billion in 2030, and to increase further to 9.7 billion in 2050 and 11.2 billion by 2100 (United Nations, 2015). It is obvious that, following this trend, there will be an increased need for food and fuel resources. Moreover, human consumption patterns are far from sustainable and have a heavy environmental burden. The relationship between sustainable development and the use of resources, fuel, food, land and water is very significant (Apaiah et al., 2006).

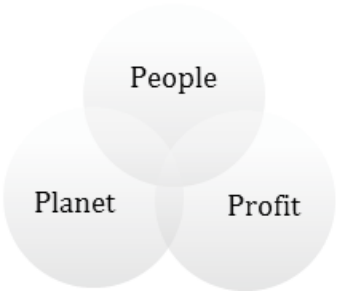

Figure 2: The three pillars of sustainability 'People, Planet, Profit'. The centre of the chart is the area of sustainable production.

As already mentioned, a shift in attitude of mind from a more prominent point of view on sustainability to a necessity resulted in a worldwide demand for sustainable products and services. The three pillars of sustainability 'people, planet, profit' (Figure 2) are helpful to understand the concept of an integrated socio-economic and environmental policy. When it comes to determining whether or not a company can claim her products or services to be sustainable, these definitions seem to be inadequate. No human actions are one hundred per cent sustainable. It is a matter of being more sustainable than the alternative.

Approaching sustainability from a more technological point of view, one can represent the latter by assuming the technosphere interacts with the ecosphere in two ways (Dewulf et al., 2000). First of all, the technosphere extracts material and energy resources from the ecosphere (resource point of view). Subsequently, waste (or low quality products as represented in Figure 3) is generated and emitted from the technosphere into the ecosphere (emission point of view). As for the definition of the Brundtland report, the future needs of mankind would be endangered if the consumption rate of the resources is higher than the rate of resource production. Otherwise, if waste is to be emitted to a higher extend, damage of the ecological mechanisms in the ecosphere can occur. In its turn, it will affect the resource production rate of the

ecosphere (Dewulf et al., 2000). These two boundary conditions can be represented by the solar driven closed cycle of materials (Figure 3).

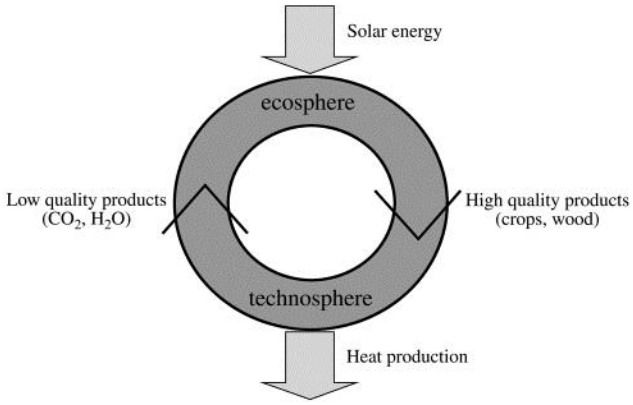

Figure 3: Solar driven closed cycle of materials. High quality products (e.g. wood) are delivered by the ecosphere whereas low quality products (CO_2, H_2O) are returned by the technosphere back into the ecosphere (together with a certain degree of heat production or dissipation) (Dewulf et al., 2000).

The first law of thermodynamics states that energy can never be lost nor created, so fossil resources could theoretically be used without any consequences. While energy cannot be lost, the quality of energy certainly can and will. The quality of the energy formed in the combustion of fossil fuels (heat), is much less than the quality of the initial energy in the fuel. As cited in the second law of thermodynamics (regarding isolated systems), the ability to do work will always decrease until equilibrium has been reached. For example, the energy (heat) in hot water is of lower quality than electrical energy. A conventional energy analysis fails to distinguish these gradations in energy quality. More detailed information about sustainability assessments and Life Cycle Assessment (LCA) will be given in Chapter 1.3 and 1.4 (Apaiah et al., 2006). As a result of the second law of thermodynamics, a certain amount of heat will be produced in an irreversible technological process. High quality products (e.g. wood) are delivered by

the ecosphere whereas low quality products (CO_2, H_2O) are returned by the technosphere back into the ecosphere (according to a certain degree of heat production or dissipation) (Figure 3).

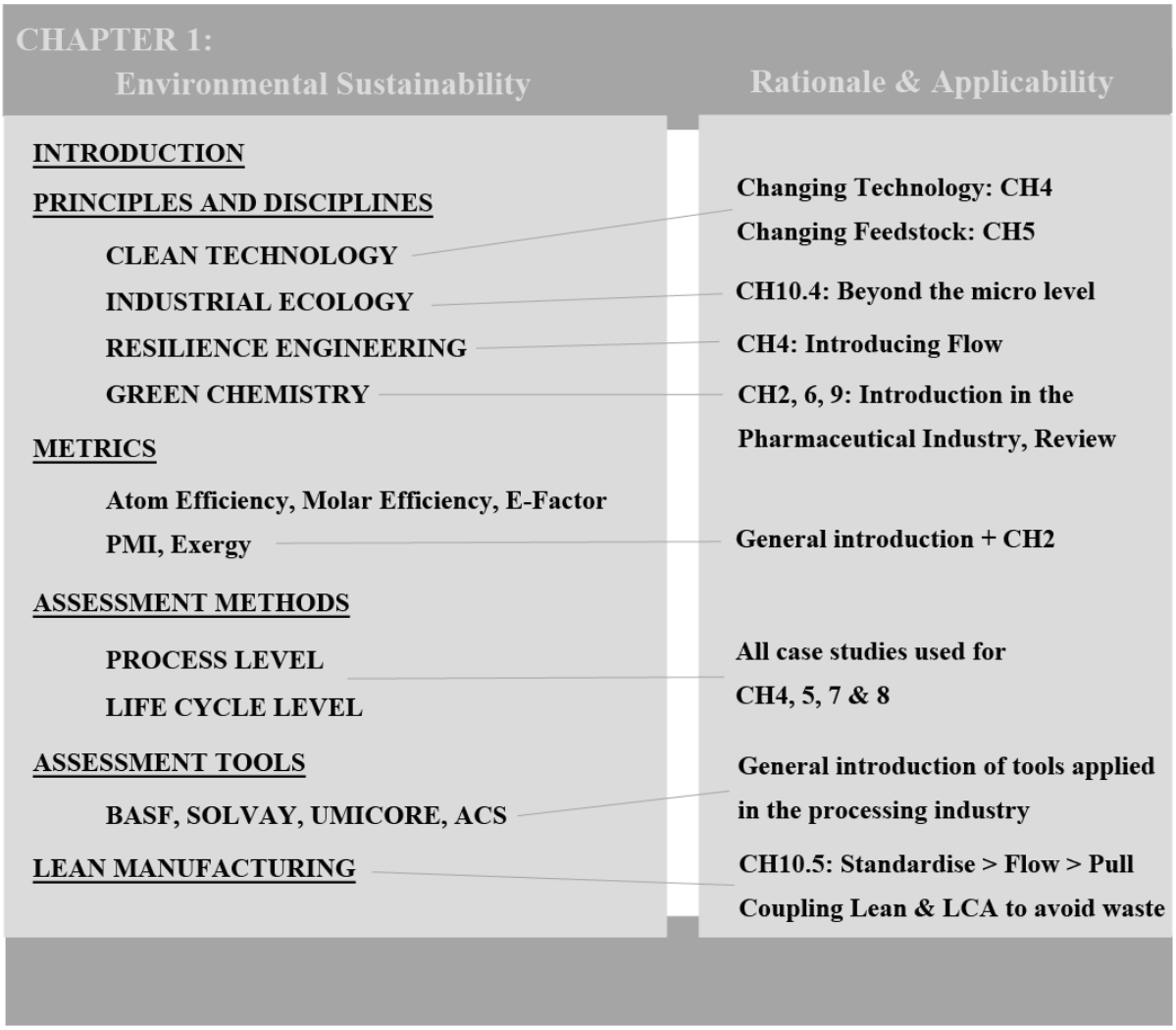

Figure 4: Rationale behind the content of Chapter 1 and its connection to other chapters and topics through this PhD thesis.

These two basic boundary conditions are incorporated in a number of concepts: Clean Technology (CT), Industrial Ecology (IE) and Green Chemistry (GC). The principles CT and GC focus on the process (product) level, while IE aims at a broader perspective: the overall industrial environment (Dewulf and Van Langenhove, 2004). These

concepts, along with a few other established principles and disciplines are shortly described in Chapter 1.2 below. The rationale of why these specific principles were chosen to be introduced here, together with the applicability of them through this PhD thesis is given in Figure 4.

1.2 Principles and disciplines

Due to the importance of environmental sustainability and sustainable development in general, especially in the processing and more specifically in the (fine) chemical and pharmaceutical industry, industries and academia started to work out several principles on how to define sustainability in production areas and how to reach this in manufacturing processes. Green Engineering (GE), being the idea that bundles all relevant, subsequent principles, should be continuously adapted. The 12 Principles of GE provide a framework for scientists and engineers to engage in when designing new materials, products, processes, and systems that are benign to human health and the environment. A design based on the 12 principles moves beyond baseline engineering quality and safety specifications to consider environmental, economic, and social factors (Anastas, 2003; Anastas and Zimmerman, 2003; McDonough et al., 2003; Anastas, 2008). Since (environmental) sustainability is an important objective in developing new technologies, it is important always being one step ahead. This type of 'Smart Engineering' is a critical factor to consider when defining an integrated sustainable policy. As economic, ecological and sociological branches are continuously evolving, GE cannot be static (García-Serna et al., 2007).

1.2.1 Clean Technology

As one of those dynamic concepts under the GE umbrella Clean Technology (CT) has been represented as "a means of providing a human benefit which, overall, uses less resources and causes less environmental damage than alternative means with which it is economically competitive" (Dewulf et al., 2000). The focus does not rely on the materials provided, but on the human benefit obtained. With the idea of economic efficiency, it goes beyond concepts as Cleaner Production (CP). One should prefer the least economic costly alternative with the least environmental cost. This idea is certainly not implemented in Clean-up Technologies, where environmental burden is suppressed 'at all costs', without changing the process in an integrated way to accomplish any financial profit. There are several ways of applying CT, however the largest share of improvement actions is to be subdivided in achieving Clean Technologies through (1) changing technology and (2) changing the feedstock, which is shortly explained below (Dewulf et al., 2010).

1.2.1.1 Changing Technology

While CT is aiming at the lowest environmental burden with the lowest economic cost, it seems logic that changing technologies through e.g. process intensification (integration of heat through heat exchangers, combined heat and power production in order to optimise the use of exhaust heat, etc.) is of high concern. These type of changes has been applied frequently in the processing industry to optimise resource consumption within factory boundaries. However, it remains challenging to integrate industrial zones such as industrial port areas etc. Waste for one producer can be a valuable feedstock for a neighbouring producer, thereby optimising the industrial metabolism. An example of

how changing technology can strive towards CT is given in Chapter 4 with the introduction of continuous manufacturing technologies compared to batch processing.

1.2.1.2 Changing the Feedstock

While the environmental cost or burden of a process, product or service certainly is at least partly the result of the converting technology (see above), it is as much a characteristic of the used feedstock for production. The environmental impact of a bio-based plastic (e.g. polymerised monomers from a crop feedstock) compared to a fossil based plastic (through the use of crude oil) can be significantly different. The very same is true in the fine chemical and pharmaceutical sector. Chapter 5 will elaborate on the use of a biological feedstock (cell culture) versus the commonly very fossil based chemical synthesis steps used in pharmaceutical manufacturing.

1.2.2 Industrial Ecology

In natural ecological systems, one assumes the presence of three theoretical types of systems: (1) linear flow through systems with energy input, unlimited resource input and unlimited waste generation; (2) quasicyclic systems with energy input, limited resource input and limited waste generation; (3) cyclic systems where energy is the only input considered and all material is being recycled (Figure 5) (Dewulf and Van Langenhove, 2004).

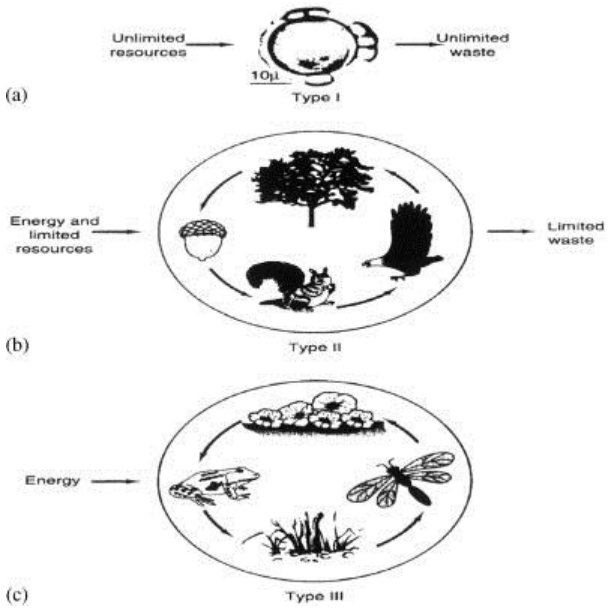

Figure 5: Three types of natural ecological systems. (a) linear flow through systems with energy input, unlimited resource input and unlimited waste generation; (b) quasicyclic systems with energy input, limited resource input and limited waste generation; (c) cyclic systems where energy is the only input considered and all material is being recycled (Dewulf and Van Langenhove, 2004).

In the concept of Industrial Ecology (IE) (1996), the overall industrial environment should be compared to a natural ecological system. The final theoretical objective is to maintain a cyclic system, where energy is the only input. To close the material loops, individual firms have to be connected into such industrial ecosystem. Therefore, reuse, recycling and waste valorisation are the basic principles of IE.

Design for Environment (DfE), which can be considered as a methodology to obtain an IE should be performed on different levels in the production process of a product or service. Design for environmental processing and manufacturing (e.g. reducing the use of hazardous chemicals), as well as design for environmental packaging (e.g. eliminating unnecessary paper or cardboard use) and design for disposal or reuse (closing the loop) is to be considered (Allenby, 1999). In the end of this PhD thesis,

Chapter 10.2 explains how DfE can be achieved using the results of this work while Chapter 10.4 elaborates in a potential research outlook what can be done beyond the micro level, touching base on the concept of IE.

The last few years, the whole concept of cyclic IE has become a top priority within European policy. In 2015, the European Commission (EC) and the Council drafted an EU action plan for the Circular Economy (CE) (European Commission, 2015a). The EC adopted the CE Package, which includes revised legislative proposals on waste to stimulate Europe's transition towards a circular economy which is designed to boost global competitiveness, foster sustainable economic growth and generate new jobs. The revised legislative proposals on waste include: the proposed Directive on Waste; the proposed Directive on Packaging Waste; the proposed Directive on Landfill; the proposed Directive on Electrical and Electronic Waste, on End-of-Life Vehicles, and Batteries and Accumulators and Waste Batteries and Accumulators. The CE Package consists of an EU Action Plan which establishes a concrete programme of action, with measures covering the whole life cycle: from production and consumption to waste management and the market for secondary raw materials (Gordeeva, 2016; Gu et al., 2016).

1.2.3 Resilience Engineering – Introducing Flow & Pull

Once such an ecosystem has taken its shape (linear flow through, quasicyclic or cyclic), this chain of effects – what is called a Supply Chain (SC) in an industrial metabolism – has a certain degree of resilience.

Integrated design of new technologies or products must be resilient rather than resistant. This way, systems are allowed to respond more correctly to unpredictable changes in variables (inputs/outputs). A material or product is called resilient if it has the capability to return to its original shape or position after stressing or deforming the latter, without exceeding its elastic limits. The very same is true for SCs. Rangeability in for instance process control indicates how far a given variable can deviate from its setpoint. More than 90% of processes in the chemical industry are based on static-stationary states, represented by energy and material balances. However, if one of the inputs has to be changed as a consequence of scarcity, the system will probably fail to adapt since it is not resilient. Resilience engineering embraces adaptation incorporated design and relates to Chapters 9.2.4 and 9.2.5 of this dissertation on Supply Chain (SC) transparency and reliability (García-Serna et al., 2007). Next, it is highly relevant in Chapter 10.5 where a multidisciplinary approach is being proposed in coupling Operational Excellence and Life Cycle Assessment (LCA) (Chapter 1.4.2).

1.2.4 Green Chemistry

Zooming in on the chemical and pharmaceutical industry, Green Chemistry (GC) introduces a concept based on a set of 12 rules containing five main principles: (1) waste minimization, (2) the use of renewable resources other than biomass, (3) eco-efficiency, (4) degradation and (5) health and safety (Glavic and Lukman, 2007). Reducing the use and generation of hazardous substances should be incorporated into the design of chemical products or processes through the selection of feedstocks (more bio-based materials), reagents, alternative reaction pathways or alternative ‘green’ solvents. Mind the connection with Chapter 1.2.2 on DfE with GC more focusing on the process itself while IE embraces the whole (industrial) ecosystem (Horvath and Anastas, 2007).

These overall Green Engineering (GE) concepts are all leading to a more sustainable development of technologies and processes without knowing the quantitative improvements towards preceding generations. Measuring methods including Life Cycle Assessment (LCA), Exergetic Life Cycle Analysis (ELCA) and emission-based methods will be indispensable in order to quantify sustainability (Chapter 1.3 and 1.4).

1.3 Metrics

1.3.1 Types of metrics

Before arriving at measuring methods and known tools in industry, a set of quantitative measuring metrics are shortly introduced in this chapter. Since no technology can be one hundred per cent 'green', adequate assessment of the 'greenness' of a technology or process is an important aspect for decision makers (Dewulf et al., 2007b). Metrics, defined in a consistent way, are important tools to quantify and allow better communication with for instance the stakeholder community. Many different classifications of metrics exist depending on the system boundaries, impact classification and time horizon, the location of the impact within the cause and effect chain, etc. (what does one actually want to quantify?). When it comes to system boundaries or the level a certain assessment method acts on, metrics can be subdivided in process oriented metrics and life cycle oriented metrics. While the latter type of indicators or metrics are acting on the process itself (not taking into account the production system of any of the inputs, neither the downstream processing of products or waste), the former are taking into account the complete (cumulative) end to end Value

Chain (VC) of a certain product or service in the industrial metabolism, starting at raw material extraction until the End-of-Life (EoL) phase (Dewulf et al., 2008; Lapkin and Constable, 2009). Earlier the concept 'Supply Chain' (SC) was introduced. Note that this is not necessarily the same as a 'Value Chain' (VC). The VC is that part of the SC that is used to create competitive advantages over similar VCs, while the SC is typically the set of operations performed to produce a product or service. In disciplines such as process engineering typically process oriented metrics are used. Note that all 12 originally formulated Green Chemistry (GC) principles were process oriented and did not include any other aspect of the VC than the process inputs and outputs themselves, in contrast to the 12 Green Engineering (GE) principles. An example that is often used at process level to evaluate resource accounting and resource efficiency is the exergy content expressed in joules of exergy (further explained in Chapter 1.3.7).

Next, metrics can be classified according to the type of environmental impact they quantify. According to the impact assessment method used, up to 18 different impact categories are to be distinguished (European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010). A typical example of a life cycle based metric within quantifying climate change is the Carbon Footprint (CF), expressed in CO_2-eq. It is clear that this emission based indicator is restricted in use to the quantification of climate change.

While the CF is a metric calculated based on the radiative forcing of the molecule of the environmental stressor compared to that of CO_2 (and clearly acts as a midpoint indicator measured in the beginning of the cause effect chain upon emission), the other side of the spectrum of indicators is damage oriented. At the end of the cause and effect chain the impact of a certain environmental stressor (e.g. a pulse of emitted CO_2) is aggregated in

a way that several midpoint impact categories (e.g. climate change, acidification, marine eutrophication, etc.) will contribute to three commonly defined endpoints or Areas of Protection (AoPs). The consensus of today is to subdivide AoPs in (1) the natural environment or ecosystem, (2) human health and (3) natural resources, whereas quite some new approaches in this fast moving field aim at tackling the postulated incompleteness and potential overlap between these AoPs (PROSUITE, 2009; Dewulf et al., 2015). The following paragraphs go back to process oriented metrics and explain the concept and usability some of the most used indicators in chemical and pharmaceutical manufacturing, related to Chapter 2.2 and Chapter 6.

1.3.2 Resource oriented Metrics: Atom Efficiency

The metric and terminology Atom Efficiency (AE) is incorporated in the second principle of Green Chemistry; "synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product" (Anastas and Warner, 1998; Lapkin and Constable, 2009; McGonagle et al., 2014).

$$AE = \frac{molecular\ weight\ of\ product}{molecular\ weight\ of\ reactants} \quad (1)$$

Traditionally, the overall efficiency of a process has been expressed in calculating the percent mass yield but the AE is of a very different concern than yield, because a high-yielding process could still result in a substantial amount of by-products. Poor atom economy or efficiency is common in the fine chemical and pharmaceutical industry (as is the Coefficient Of Performance (COP, introduced in Chapter 4.3.3).

1.3.3 Resource oriented Metrics: Molar Efficiency

While AE focusses very much on the reactants incorporated in the final molecule/product and not on other inputs such as solvents, catalysts, etc., the Molar Efficiency (ME) can be expressed as follows according to McGonagle et al., 2014:

$$ME = \frac{moles\ of\ product}{moles\ of\ sm + moles\ of\ add + moles\ of\ cat + moles\ of\ solv} \quad (2)$$

where sm stands for starting material or building blocks, add for additives, cat for catalysts and $solv$ for solvents respectively. The metric creates the ability of focusing on more than building blocks, opening the door to metrics for a circular economy in the quantification of waste as a resource (e.g. used solvents).

1.3.4 Resource oriented Metrics: E-Factor

Taking that thought one step further, there is the E-Factor which compares the mass of product to the mass of waste generated within a certain process. It accounts for all raw materials and waste associated with a unit operation. It should be noted that a variety of less inclusive E-Factor calculations (e.g., based solely on the solvent consumption) can also be used for a more convenient analysis, which leads to multiple E-Factors (Lapkin and Constable, 2009; McGonagle et al., 2014). This factor and others are evaluated for the fine chemical and pharmaceutical industry specifically in Chapter 2.2. The equation of the E-Factor is given below:

$$E - Factor = \frac{mass\ of\ waste}{mass\ of\ product} \quad (3)$$

1.3.5 Resource oriented Metrics: PMI

Curzons and colleagues disclosed the Process Mass Intensity (PMI) and Reaction Mass Efficiency (RME) metrics, both of which relate the mass of constituents used in a particular reaction to the mass of product formed. The PMI compares masses of reactants to product but did originally not account for the solvent used in a reaction. However, just as is the case with the E-Factor, less inclusive, recent PMI calculations (e.g., based on solvent consumption levels) can also be used for a more convenient analysis, which leads to multiple PMIs (Lapkin and Constable, 2009; McGonagle et al., 2014). These type of metrics have been broadly useful as quantitative measures with which to assay individual reactions and overall processes. Indeed, indices such as PMI have been instrumental in advancing the sustainability of pharmaceutical processes, with PMI highlighted as the preferred metric aimed to drive greater efficiencies in pharmaceutical syntheses which will be elaborated in Chapter 2.2 and Chapter 6. The calculation of the PMI is given below (Lapkin and Constable, 2009; McGonagle et al., 2014):

$$PMI = \frac{mass\ of\ waste}{mass\ of\ product} = E - Factor + 1 \qquad (4)$$

1.3.6 Resource oriented Metrics: RME

As stated in the previous paragraph, the Reaction Mass Efficiency (RME) relates the mass of constituents used in a particular reaction to the mass of product formed. More

specifically, the RME compares the mass of the product to the total mass of reactants. It can mathematically be expressed as follows:

$$RME = \frac{mass\ of\ product}{mass\ of\ reactants} \quad (5)$$

1.3.7 Resource oriented Metrics: Exergy

1.3.7.1 The concept of exergy

Another resource oriented metric that will be more extensively elaborated in the work since it will be used in the more research related sections is exergy. Energy as such can never be lost nor created, nevertheless, the amount of useful energy or marketplace energy is not conserved. The concept of energy used in industrial settings, the ability to cause change, is in fact what is understood by the concept of exergy. The amount of exergy (Ex) can be defined as the amount of useful work that can be obtained from a system in equilibrium with its surroundings through reversible processes only (Dewulf et al., 2008). It has been justified (Gouy and Stodola, 1910) that the absolute value of exergy loss (Ex_{loss}) equals the product of entropy production (S_{gen}) and reference temperature (T_0) (Koroneos et al., 2003).

$$Ex_{loss} = T_0 \times S_{gen} \quad (6)$$

1.3.7.2 Different types of exergy

The total exergy of a system can be itemized into four different types of exergy: (1) 'physical exergy' (related to the temperature and pressure differences of the system); (2) 'chemical exergy' (due to the chemical composition of the system compared to that of

the reference environment); (3) 'kinetic exergy' (proportional to the velocity difference between the system and its reference state); (4) 'potential exergy' (due to the relative elevation of the system) (Tsatsaronis, 2007):

$$Ex_{sys} = Ex_{sys}^{PH} + Ex_{sys}^{CH} + Ex_{sys}^{KN} + Ex_{sys}^{PT} \quad (7)$$

The subscript 'sys' is used to demonstrate the association with the exergy of the system as a whole instead of a material stream (no subscript).

The physical exergy of a system can be expressed as follows:

$$Ex_{sys}^{PH} = (U - U_0) + p_0 \times (V - V_0) - T_0 \times (S - S_0) \quad (8)$$

U, U_0, p_0, V, V_0, S and S_0 represent respectively the internal energy, the internal energy of the reference state in thermodynamic equilibrium, the pressure of the reference state in thermodynamic equilibrium, the volume, the volume of the reference state in thermodynamic equilibrium, the entropy and the entropy of the reference state in thermodynamic equilibrium.

According to the two contributions to the physical exergy of a system, the latter consists of 'mechanical exergy' (associated with system pressure along the isothermal line at T_0) and 'thermal exergy' (associated with system temperature along the isobaric line at p_0):

$$Ex_{sys}^{PH} = Ex_{sys}^{T} + Ex_{sys}^{M} \quad (9)$$

While for a material stream, the total exergy can be described as

$$Ex = Ex^{PH} + Ex^{CH} + Ex^{KN} + Ex^{PT} \tag{10}$$

With Ex^{KN}:

$$Ex^{KN} = \frac{1}{2} \times m \times \bar{v}^2 \tag{11}$$

and Ex^{PT}:

$$Ex^{PT} = m \times g \times z \tag{12}$$

m, $\bar{v}$, g and z denote respectively the mass of the material stream, the velocity of the matter relative to the environment, the gravitational acceleration and the elevation height relative to the reference environment.

The physical exergy of a material stream can be expressed as follows:

$$Ex^{PH} = (H - H_0) - T_0 \times (S - S_0) \tag{13}$$

With

$$H = U + p \times V \tag{14}$$

$$dH = dU + d(p \times V) = dU + p \times dV + V \times dp \tag{15}$$

$$dU = T \times dS - p \times dV \tag{16}$$

H, H_0, p and T are the enthalpy, the enthalpy of the reference state in thermodynamic equilibrium, the pressure and the temperature of the material stream respectively.

The physical exergy can also be expressed as the sum of the mechanical and thermal exergy of a stream of matter:

$$Ex^{PH} = Ex^{T} + Ex^{M} \tag{17}$$

The chemical exergy of a material stream can be denoted as follows (Bilgen et al., 2007):

$$Ex^{CH} = n \times \left[\mu - \mu_0 + R \times T_0 \times n \times \ln\frac{C}{C_0}\right] \tag{18}$$

where n is the number of moles, μ the chemical potential, μ_0 the chemical potential of the reference state (in equilibrium with its surroundings), R the gas constant, C the concentration and C_0 the concentration of the reference state in thermodynamic equilibrium. When the material stream consists of several, different substances, one obtains (Bösch et al., 2006):

$$Ex^{CH} = \sum n_j \times ex_j^{CH} \tag{19}$$

$$ex^{\circ CH}_{\ j} = \Delta_f G^{\circ}_{\ j} + \sum_{el} n_{el} \times ex^{\circ CH}_{el} \tag{20}$$

with n_j the mole fraction of substance j in the material stream, ex_j^{CH} the molar chemical exergy of substance j (approximated by $ex_j^{\circ CH}$, the standard molar chemical exergy of substance j), $\Delta_f G^\circ{}_j$ the standard Gibbs free energy of formation of substance j, n_{el} the number of molecular elements of substance j and $ex_{el}^{\circ CH}$ the standard partial molar chemical exergy of molecules of substance j.

'Thermal exergy' (concept used to quantify the exergetic content of energy carriers) is represented by a Carnot cycle (Bösch et al., 2006):

$$Ex^T = Q_h \times \frac{(T_h - T_0)}{T_h} \tag{21}$$

with Q_h the energy of the heat source, T_h the temperature of the heat source and T_0 the temperature of its surroundings, being the reference state.

1.4 Assessment Methods

1.4.1 Methods at the Process Level: Exergy Analysis

Amini et al. (2007) presented the main purpose of Exergy Analysis (EA) as to detect and evaluate the causes of thermodynamic imperfection of a process in a quantitative way (see Figure 6). Knowing its imperfections, one can improve the thermodynamic performance of a process by choosing the right alternative (Amini et al., 2007). As mentioned earlier (Chapter 1.3.1), the concept of exergy brings about an excellent tool to quantify both material resource consumption and energy requirement in one single

unit, based on the principles of thermodynamics. Not only is EA an important tool to assess the environmental impact of a product or service, it is also useful in providing optimum designs and operation conditions (Bilgen et al., 2007). Given the triple bottom line of sustainability, the purpose of EA in improving cost effectiveness is highly discernible. All resources are, to some degree, finite, illustrating the connection between economical scarcity and resource depletion (environmental burden) (Bilgen et al., 2007).

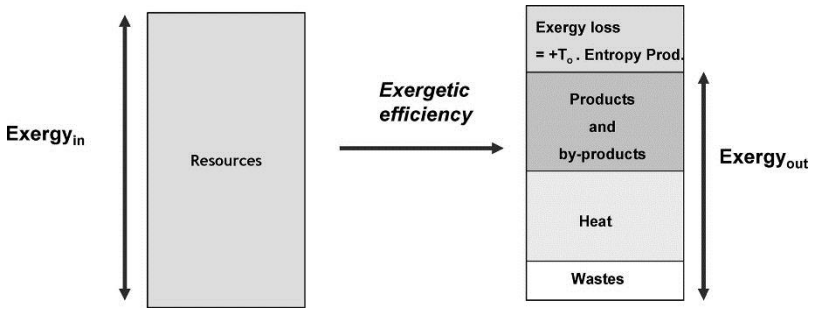

Figure 6: Second Law analysis of a real process: the entropy of an isolated system always increases over time, or remains constant in the ideal cases where the system is in a steady state or is undergoing a reversible process (Dewulf et al., 2008).

1.4.2 Methods at the life cycle level: Life Cycle Assessment

While EA is an example of a process oriented assessment method, Life Cycle Assessment (LCA) is an analysis of the cumulative environmental impact of a product or service taking into account its complete life cycle in the industrial metabolism (from the extraction of raw materials to the very End of Life, EoL phase). A complete Life Cycle Assessment consists of four coherent and iterative stages: (1) definition of the goal and scope; (2) Life Cycle Inventory (LCI); (3) Life Cycle Impact Assessment (LCIA); (4) interpretation of the obtained results. The first step to accomplish is to define the goal and scope (among others system boundaries and functional unit). Subsequently

an LCI is performed, aiming at describing the environmentally relevant physical and energetic flows or environmental stressors to and from the technosphere (Russell et al., 2005). This data collection is the most time-consuming part and is at least equally important as the assessment itself. A relatively modest part of the industrial processes and involved chemicals have been registered into life cycle databases (e.g. ecoinvent) (Jiménez-González, 2000). One of the most prominent shortcomings to current LCA methodologies is the balancing of different environmental stressors in different impact assessment categories, which may all be quantified in a different way. Being one of the main tools in sustainability assessments of industrial processes or products, LCA takes into account most of the known ecological effects on the ecosystem (interacting with the overall industrial environment or technosphere) and the population endangering the possibilities of current and future generations (after Brundlandt's sustainability definition) (Dewulf and Van Langenhove, 2002). In order to quantify the impact on the ecosphere, one has to consider the whole life cycle of a product. This typically leads to a cradle-to-grave (or in a more circular economy line of thought cradle-to-cradle, see the cyclic ecosystem in Chapter 1.2.2) approach. All stages of an LCA can possibly be performed by different operators with different interpretations, leading to rather subjective results. Many initiatives have been taken in order to harmonise LCA methodologies and make it a more objective tool (Russell et al., 2005). In LCA, the calculation of depletion of natural resources is rather debatable. Usually, a distinction is made between the use of minerals and metals and the use of fossil resources. The fact that depletion of minerals actually cannot take place because of the mass conservation law raised several questions about this concept. On the other hand, according to the second law of thermodynamics the quality of rich ores of different minerals or metals can be and will be lost during its life cycle. This loss can be measured by introducing the exergy concept into LCA (Cornelissen and Hirs, 2002; Finnveden et al., 2009;

Valero and Martinez, 2010; Drielsma et al., 2016; Finnveden et al., 2016; van Oers and Guinee, 2016).

In an Exergetic Life Cycle Analysis (ELCA), the localization and identification of losses of natural resources through the life cycle of a product or service takes place. It is a more protruding way of design, since better proposals for reducing the loss of natural resources can be obtained. Examples of ELCA methods are the Cumulative Exergy Demand (CExD) (Bösch et al., 2006) and the Cumulative Exergy Extraction from the Natural Environment (CEENE) (Dewulf et al., 2007a; Zhong et al., 2016). An ELCA is a clear example of a resource based LCA that aims at avoiding losses through the Supply Chain (SC), optimising production efficiencies and turning residual waste into resources in striving towards a circular economy.

1.5 Assessment Tools in Processing Industry

Before touching upon applied sustainability assessment in the pharmaceutical sector, some environmental sustainability assessment tools, developed in industry are shortly introduced below. According to the SAMT (Sustainability Assessment Methods and Tools to support decision-making in the process industries) Horizon 2020 project, 52 methodologies and 38 tools were designed in the processing industry until today (Pajula, 2016). Four tools, developed at BASF, SOLVAY, UMICORE and the American Chemical Society (ACS) are exemplified underneath.

1.5.1 BASF: Eco-efficiency Analysis

BASF created the tool of eco-efficiency analysis to address not only strategic issues, but also issues posed by the marketplace, politics and research. It serves as an enabling decision-making tool for processing industries visualising in a transparent way life cycle costs and ecological results in order to establish an eco-efficiency portfolio. This concept is very much related to the Clean Technology (CT) concept that has been elaborated in Chapter 1.2.1. The results within the tool are summarised through weighting factors evaluating alternatives of a customer defined benefit over the whole life cycle (Saling et al., 2002). The tool is a helpful, analytical tool in R&D as well as in continuous improvement to eventually obtain more sustainable processes and products (Saling et al., 2002).

1.5.2 SOLVAY: SPM and Sustainability Screening Sites (S3S)

Two tools have been developed at Solvay: (1) the Sustainable Portfolio Management (SPM) and (2) the Solvay Sustainability Screening Sites (S3S). The necessity to both minimize the potential negative impact and enable appropriate allocation of resources to capture opportunities at the marketplace drove the development of SPM at Solvay. Business opportunities and investment strategies include a sustainability challenge that encompasses an exhaustive SPM analysis (Bande and Debecker, 2012). All business units are carefully consulted with in-house experts from strategy, product stewardship, marketing, technical services, etc. Solvay has developed a unified methodology called S3S (Solvay Sustainability Screening Sites) to help making decisions about future industrial sites. 43 indicators covering all aspects of industrial sustainability are measured (Bande and Debecker, 2012). In the end the tool and generated reports contribute to the evaluation of the sustainability of the industrial sites of Solvay.

1.5.3 UMICORE: Assessment of Product and Services Sustainability (APS)

Umicore's believe to have a full understanding of the impact of its products from an ecological, societal and economic viewpoint resulted in investments aiming at a better understanding of life cycles of products depending on the competitive advantage of certain applications. The tool that was developed making these efforts is called Assessment of Product (and services) Sustainability (APS) of which its methodology consists of a set of qualitative indicators (through 58 preformatted questions) and quantitative weighting factors around eight themes. Based on a set of flagship products and services, the business provided input for the Horizon 2020 sustainability objectives of the enterprise, taking into account the understanding and knowledge on sustainability of its Value Chains (VCs) (Umicore, 2015).

1.5.4 American Chemical Society: FLASC™

In contrast to the three aforementioned tools of BASF, Solvay and Umicore, the Fast Life Cycle Assessment of synthetic Chemistry tool (FLASC™) was developed by a sector federation rather than a single enterprise, though its development was heavily supported by GlaxoSmithKline (GSK) (Curzons et al., 2007). Leading members of the American Chemical Society (ACS) Pharmaceutical Roundtable (PR) such as GSK, DSM and BMS developed the tool (Curzons et al., 2007; Jiménez-González et al., 2013). Life cycle inventory (LCI) data for approximately 140 materials were generated and collated using the eight core GSK 'sustainability metrics' impact categories. In order to come to 14 unique material classes of impact profiles, principal component analysis was used. Using these Life Cycle Inventories (LCIs) typical batch profiles could be obtained for synthesising a GSK Active Pharmaceutical Ingredient (API). In the end, the

development led to a series of formulas that enabled impact scoring for eight impact categories, averaged out into the FLASC™ score (Curzons et al., 2007; Jiménez-González et al., 2013).

1.6 Lean Manufacturing

As was the case for BASF, Solvay, Umicore and the pharmaceutical industry, minimising waste and optimising production efficiencies is key, but turning those Life Cycle Thinking (LCT) concepts in daily manufacturing business is all but obvious. Little process engineers will look from a life cycle point of view at their production line. It is on the manufacturing floor that inefficiency starts and change is needed. In the processing industries – more specifically the Added Value Manufacturing (AVM) industries such as the pharmaceutical industry – continuous improvement is an important aspect of process engineering. One of the toolboxes used to improve efficiencies, reduce waste and strive towards Operational Excellence (OE) is Lean manufacturing. Lean found its roots in the Japanese Toyota Production System (TPS) during the late eighties and is essentially an operational management technique to create value for customers and therefore reducing all Non Value Adding processes (NVA) or waste in industry. It is a set of tools such as Value Stream Mapping (VSM), Just in Time (JIT), pull production (introduction of flow or continuous operations), visual management, etc. to essentially reduce 'the three Ms' Muri, Muda and Mura or overburden, waste and unevenness (Crabtree, 2010). Overburden can lead to failures in production and is to be avoided. In its broader sense, waste comprises overproduction, overprocessing, transport, movement, waiting, reprocessing, stock and misuse of talent. All of these operations are NVA processes and will not add to the willingness to pay of

any customer, hence the value of a product or service. Unevenness or variability in production through e.g. a production planning that is not meeting the demand or a series of unit operations with very different cycle times can lead to extra stock, waiting, movement and eventually higher lead times (Bicheno and Holweg, 2009). Essentially the goal of Lean and resource based LCA is (at least partly) the same: creating more value with less resources, doing more with less.

Chapter 2
Sustainability in the Pharmaceutical Industry

Partly redrafted from:

De Soete, W., Jiménez-González, C. et al. (2016). "Challenges and Recommendations for Environmental Sustainability Assessments of Pharmaceutical Products in the Healthcare Sector." Green Chemistry **submitted**.

2.1 Introduction

Following a broad introduction in Chapter 1, this chapter zooms in on sustainability practices in the pharmaceutical industry specifically, starting with an introductory framework of the need for sustainable innovation in the sector. 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 (World Health Organization, 2015). In Europe, overall healthcare expenditure expressed as percentage of the GDP increased from 8.2% in 2007 to 8.8% in 2012 (OECD/EU, 2014). Following the European Commission's (EC) Directorate-General (DG) Health and Food Safety's European Core Health Indicators (ECHI), public sector spending increased from 5.9% of the GDP to 6.6% in 2012 (EC Directorate General for Health and Consumers (DG SANCO), 2013). These are revealing and significant findings since public expenditures have only been decreasing in relation to the GDP since the economic crisis of 2009 (EUROSTAT, 2016). 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 (OECD/EU, 2014). 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 (World Health Organization, 2015). 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 (Statista, 2016).

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) (Kümmerer, 2008). 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 (Thiel et al., 2015).

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 Programs FP7 and Horizon2020 and the Knowledge and Innovation Community (KIC) on Health from the European Institute for Innovation and Technology (EIT) (Meadows and Meadows, 2007). 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 (EIT Raw Materials, 2015). 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 (Malthus, 1798; Meadows and Meadows, 2007; Sfez et al., 2016). 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 development that meets the needs of mankind preserving the needs of our future generations, decoupling becomes an inherent characteristic of sustainable development (Meadows and Meadows, 2007). 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 (OECD/EU, 2014; EFPIA, 2015; Sfez et al., 2016).

2.2 A glance at the state of the art

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 (DF) production (secondary manufacturing), packaging, distribution and logistics and the End-of-Life phase (pharmaceuticals in the environment). Metrics can roughly be subdivided between process-oriented metrics and life cycle oriented metrics (Lapkin and Constable, 2009; Sfez et al., 2016). Green chemistry principles started to create visibility within the sector with publications of Pfizer, GlaxoSmithKline (GSK) and Johnson & Johnson (JNJ) in the late nineties early 2000 (Jiménez-González, 2000; Constable et al., 2001; Constable et al., 2002; Dunn et al., 2004; Jiménez-González et al., 2004b; Jiménez-González et al., 2004a; Constable et al., 2007; Curzons et al., 2007; Van der Vorst et al., 2009b; De Soete et al., 2013; Van der Vorst et al., 2013). In 2005, the formation of the 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. The foundation of the UK's National Health Service (NHS) Sustainable Development Unit (SDU) in 2008 and the subsequent focus on 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, Jimenez-Gonzalez et al. in 2014 and Kralisch et al. in 2015. 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 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 is commonly being processed from several published studies. Unfortunately, a considerable amount of efforts done 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. Chapter 6 of this PhD dissertation takes the concept of reviewing and adding to the state of the art through identifying the needs, debottlenecking and defining perspectives from and to the sector one step further.

A thorough literature review was performed of which a condensed version is presented in this chapter. For this, the Web of Science™ from Thomson Reuters™ was used. As time window, publications ranging from January 1997 until 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 Annex A1. The query 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 a 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 literature is to be found in Annex A1, together with all categories (e.g. types of publication: 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 below. Figure 7 illustrates that reasoning for the selected articles within the category of Green Chemistry (GC) related to pharmaceutical production. Figure 7a shows for all categories that the Impact Factor (IF) per year is all but correlated with the amount of citations per year of a certain article. In Figure 7b, 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 IF range between 2.5 and 8.3 where selected, all of them being comprehensive reviews or perspective articles with recommendations.

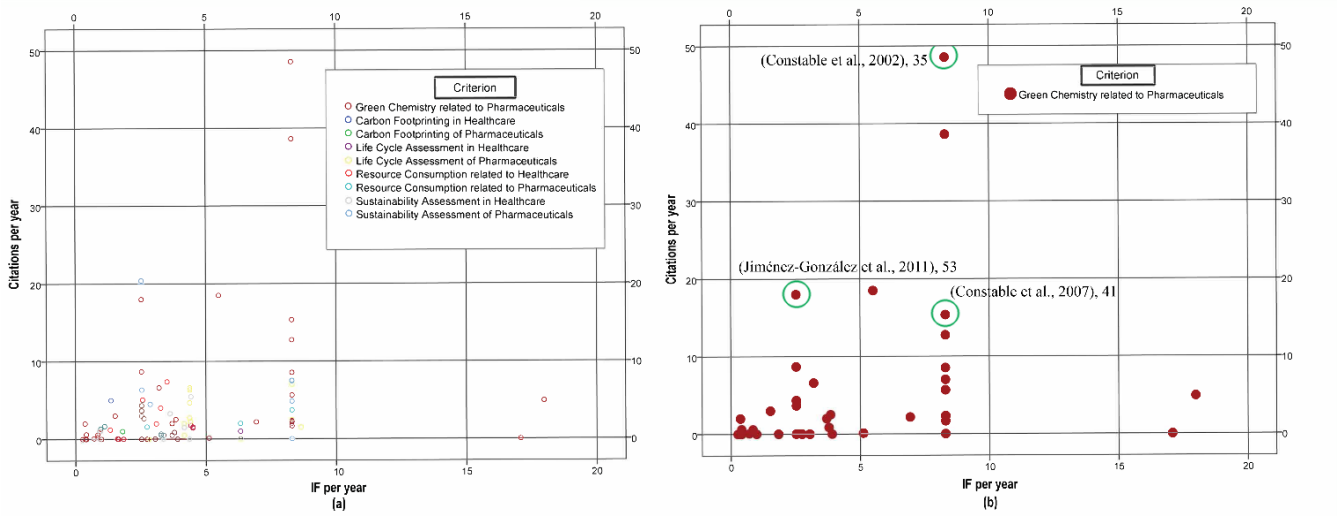

Figure 7: (a) Shows for all categories that the Impact Factor (IF) per year is all but correlated with the amount of citations per year of a certain articles. In (b), it becomes clear that the highest citations are obtained through the type of article: perspective or review article with recommendations, rather than with publishing in a journal with a high IF. In the field of Green Chemistry, three of the most cited papers within IF range between 2.5 and 8.3 where selected, all of them being comprehensive reviews or perspective articles with recommendations.

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.

Table 1: References used for literature review per topical search criterion.

Topic search criterion	References
Sustainability Assessment of Pharmaceuticals	(Wernet et al., 2009) (Jiménez-González and Woodley, 2010) (Schneider et al., 2010) **(Jiménez-González et al., 2011)** (Jiménez-González et al., 2013) (De Soete et al., 2013) (Woodley et al., 2013) (Szekely et al., 2014)

Sustainability Assessment in Healthcare	(Briggs, 2003) (Martin et al., 2009) (Boholm and Arvidsson, 2014) (Carmen Carnero, 2015) (Castro et al., 2015a) (Castro et al., 2015b) (Debaveye et al., 2016) (Marsh et al., 2016)
Life Cycle Assessment of Pharmaceuticals	(Jiménez-González, 2000) (Jiménez-González et al., 2004a) (Curzons et al., 2007) (Kim et al., 2009) (Wernet et al., 2010) (Igos et al., 2012) (Alfonsín et al., 2014) (De Soete et al., 2014b) **(Jimenez-Gonzalez and Overcash, 2014)** (Perez-Lopez et al., 2014) (Brunet et al., 2014) (Ott et al., 2014) (Ramasamy et al., 2015) (Cespi et al., 2015) **(Kralisch et al., 2015)** (Ott et al., 2016)
Life Cycle Assessment in Healthcare	(Campion et al., 2012) (Thiel et al., 2015)
Green Chemistry related to Pharmaceuticals	(Curzons et al., 1999) (Curzons et al., 2001) **(Constable et al., 2002)** (Haswell and Watts, 2003) (Nisiwaki, 2003) (Thomas and Raja, 2005) (Koel and Kaljurand, 2006) (Tucker, 2006) **(Constable et al., 2007)** (Fortunak et al., 2007) (Khetan and Collins, 2007) (Kuemmerer, 2007) (Alfonsi et al., 2008) (Cue and Zhang, 2009) (Fortunak, 2009) (Garcia-Reyes et al., 2009) (Molina-Diaz et al., 2010) (Broxterman et al., 2011) (Hartman et al., 2011) (Wernet et al., 2011) **(Jiménez-González et al., 2011)** (Joshi et al., 2011) (Soundarrajan et al., 2011) (Kaur et al., 2012) (Ley, 2012) (Watson, 2012) (Ciriminna and Pagliaro, 2013) (Dunn, 2013) (Federsel, 2013) (Leahy et al., 2013) (Osorio et al., 2014) (Rastogi et al., 2014) (Banimostafa et al., 2015) (DeVito et al., 2015) (Gupta and Mahajan, 2015) (M'Hamed, 2015) (Roschangar et al., 2015) (Sullivan, 2015) (Tucker, 2015) (Voorhees, 2015) (Gallou et al., 2016) (Borukhova et al., 2016)
Resource Consumption related to Pharmaceuticals	(Van der Vorst et al., 2009a) (Van der Vorst et al., 2009b) (Van der Vorst et al., 2010) (Van der Vorst et al., 2011) (Van der Vorst et al., 2013) (De Soete et al., 2014a)

Resource Consumption related to Healthcare	(Hatoum et al., 1998) (Optenberg et al., 2002) (Alvarez et al., 2004) (Daskalaki et al., 2007) (Manca et al., 2008) (Leekha et al., 2009) (Gonzalez-Cortes et al., 2011) (Gagliardino et al., 2012) (Polatli et al., 2012) (Roggeri et al., 2014) (Castro et al., 2015b) (Martyn et al., 2015)
Carbon Footprinting of Pharmaceuticals	(Connor et al., 2010) (Gatenby, 2011) (Lim et al., 2013)
Carbon Footprinting in Healthcare	(Connor et al., 2011) (Wormer et al., 2013) (Holmner et al., 2014) (Pollard et al., 2014)

Based on their number of citations and evaluation by experts (resulting from the expert interviews conducted in this PhD project and further elaborated in Chapter 6.3.1), six milestone papers were selected (represented in bold in Table 1 or in blue in Annex A1 for the full details). 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 mensuare' or 'measuring is knowing', the type of indicators used to measure the 'greenness' of fine chemicals and pharmaceuticals and their production routes and technologies has 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 (Constable et al., 2002). 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 member of the American Chemical Society (ACS) Green Chemistry Initiative Pharmaceutical Roundtable (GCIPR) (Anastas and Warner, 1998;

Constable et al., 2002). GSK evaluated the Reaction Mass Efficiency (RME) (the ratio of the sum of the product masses and the sum of the reagent 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 (Constable et al., 2002). 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 (Lapkin and Constable, 2009). 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 focussing 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 (Jimenez-Gonzalez et al., 2011). 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 other, a process-based hotspot analysis revealed the very high burden of solvents (up to 56%) in the production of Active Pharmaceutical Ingredients (APIs). 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 metric correlating with societal impacts focussing on the process level (Jimenez-Gonzalez et al., 2011). 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 ones in streamlined assessments (Jiménez-González et al., 2013; Cespi et al., 2015). Although there had 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 (FLASC™) tool from GSK (Curzons et al., 2007). 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 (focusing on solvent themes) 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 (Constable et al., 2007). 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 that 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).

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 et al. published "The evolution of life cycle assessments in pharmaceutical and chemical applications – a perspective" (Jimenez-Gonzalez and Overcash, 2014). 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 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)) (Jimenez-Gonzalez and Overcash, 2014). In the tutorial review by Kralisch et al. in 2015, more methodological aspects are touched upon (Kralisch et al., 2015). 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 e.g. for nanomaterials) for MCDM in early stage development. Alternative energy sourcing, green solvents and introducing flow remain key within the principles of GC and process intensification (Kralisch et al., 2015).

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. Depending on the targeted disease (chronic or acute) and the care pathway, the results may vary significantly (Debaveye et al., 2016). 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 (Penny et al., 2015).

Chapter 3
Objectives and Outline of the Dissertation

This PhD dissertation is essentially composed out of 4 main parts, subdivided in 10 chapters as presented in Figure 8. **PART 1** provides an introduction to the reader on a variety of related topics to environmental sustainability and pharmaceuticals. An overall introduction on sustainability, some of its principles and disciplines, metrics, assessment methodologies and Lean manufacturing are given in **Chapter 1** (De Soete, 2012; De Soete et al., 2013). With a study that was performed at the European Commission's Joint Research Centre (JRC), Institute of Environmental Sustainability, Ispra, Italy, **Chapter 2** illustrates the state of the art of sustainability assessment in the pharmaceutical industry through a comprehensive literature review (De Soete, 2016). Following this generic and applied introduction to part 2 and 3, **Chapter 3** gives the overall outline and connection of the different chapters of the dissertation and their objectives.

PART 2 assesses the environmental sustainability in the pharmaceutical industry. Both chemical synthesis of so-called Small Molecules (SMs) and biologicals or Large Molecules (LMs) such as proteins are within scope. A combined resource and emission based Life Cycle Assessment of batch versus continuous tabletting processes is presented in **Chapter 4** (De Soete et al., 2013). First, the aim is to quantify the environmental impact of introducing continuous processing or flow as one of the measures of process intensification and Lean manufacturing. Second, the resource footprint of the SM that acts as the Active Pharmaceutical Ingredient (API) in the tablet is generated and recommendations for further optimisation are given. Years of research have indicated that the resource footprint of SMs are dominated by fossil resources (use of organic solvents, electricity consumption for mixing and heating, etc.). **Chapter 5** compares the footprint of chemically produced SM medicines and so-called biologics (in this case Monoclonal Antibodies, MABs) (De Soete et al., 2016b). Are biotechnologically produced medicines 'greener' than conventional pharmaceuticals?

Does the dependency on fossil resources decrease for biologics? Can we expect a higher share of biotic renewables resources and land use? These questions are answered in Chapter 5. Next, since biologics have a very different mode of action and are typically parenterals (administered through injection in the bloodstream), the assessment is not just performed at compound level but rather on a technology platform level and on a yearly treatment level as well.

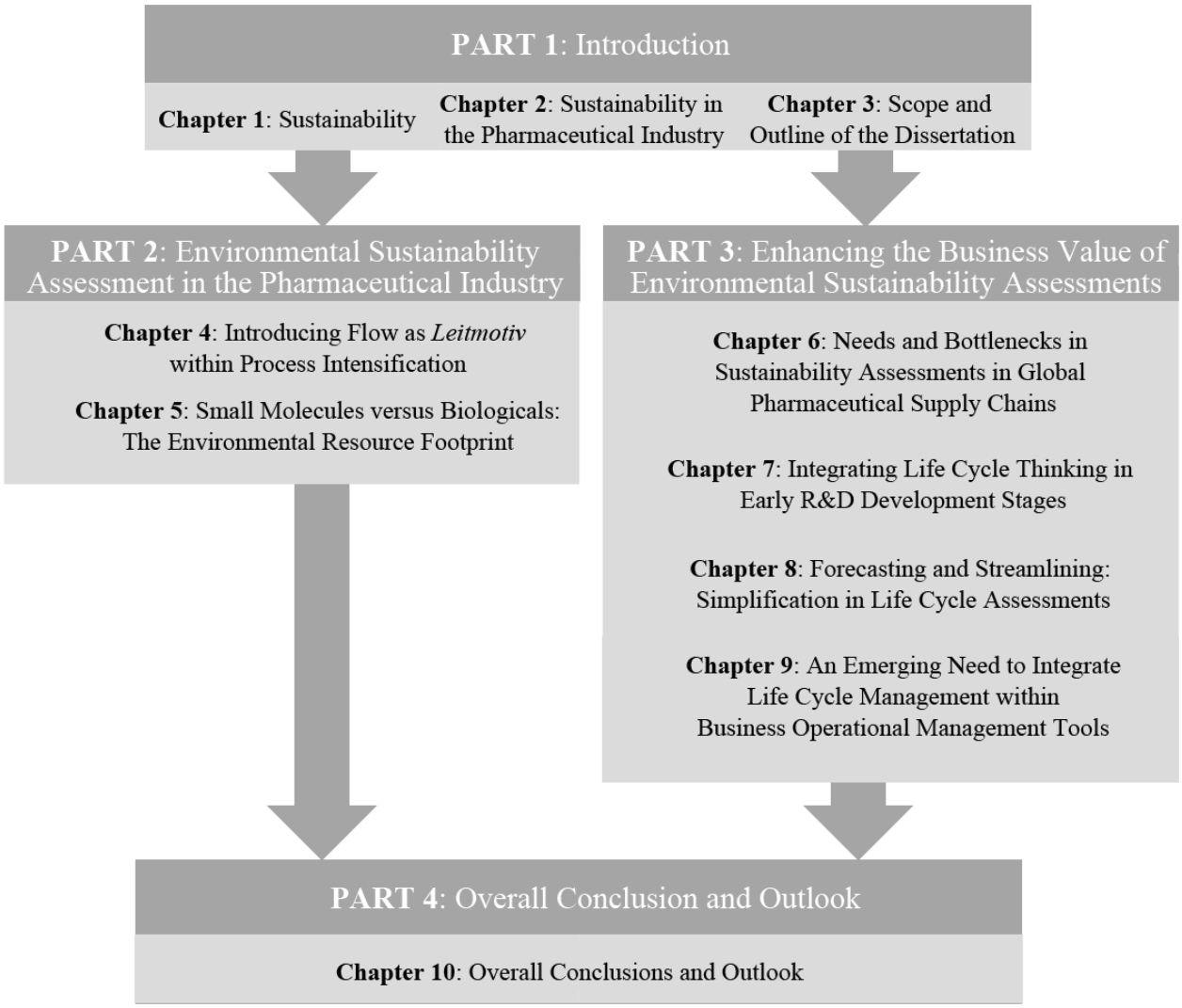

Figure 8: PhD dissertation outline and connection of the 4 parts and 10 chapters.

It is often difficult to persuade higher management of the business value of LCAs or environmental sustainability assessments in general. Experience learns that the results

are often not fully valorised and are not penetrating the daily operations. While part 2 is mainly composed out of assessments based on predefined cases, **PART 3** extracts and combines those aspects of environmental engineering, environmental sustainability assessments and Operational Excellence (OE) adding value to businesses, decision makers, policy, etc. To begin part 3 with, **Chapter 6** identifies needs and bottlenecks for environmental sustainability assessments in global pharmaceutical supply chains (De Soete et al., 2016a). Next to literature analysis that is often used to shape the state of the art, the sector needs to be connected, work together and formulate current shortcomings and future challenges. Expert interviews and stakeholder surveys were conducted during the study at the EC JRC to define the needs and bottlenecks in Chapter 6. In total, more than 300 stakeholders from predefined categories were consulted. Finally, a seminar on Sustainable Development in the Healthcare and Pharmaceutical Sector (SDHP) was organised at the JRC in Italy to connect stakeholders and define future challenges. The next chapters deal with specific key challenges (explained below) and propose solutions as visualised in Figure 8. **Chapter 7** introduces the concept of experience curves (effect of learning and upscaling) of technologies and the use of these in R&D environments to anticipate on environmental burden once a technology is at full scale production (De Soete et al., 2014a). This way, environmental indicators can be introduced in R&D decision trees or so-called stage gating processes within development. Nonetheless, data inventory within LCA is a very time consuming process and often data is lacking (especially in R&D environments because data is simply not available yet). In manufacturing environments, data is often measured but very hard to get due to data management systems that are not built for the inventory of data needed to perform LCA (temperatures, flow rates, utility consumption rates, etc.). That is why **Chapter 8** provides a set of regression formulas to forecast on the environmental sustainability of API synthesis steps based on a very limited set of predictor variables

that are in many cases readily available (1 to 5) (De Soete et al., 2014b). Can we use these correlations to predict the environmental footprint of API synthesis steps to a fair extent in terms of uncertainty? Can we come to an optimal degree of model complexity versus model uncertainty and transparency? If so, can we recommend steps for implementation within existing data systems? **Chapter 9** discusses potential bottlenecks in the integration of process modelling in Enterprise Resource Planning (ERP) system (De Soete, 2016). Why is it so hard to implement and automate environmental sustainability assessments? If a lot number can automatically be printed on a label on the folding box, why not the Carbon Footprint? Chapter 9 not only discusses the difficulties for implementations but proposes a framework in which customised ERP modules play a role in providing corporate and product sustainability assessments. To end with, **PART 4** provides an overall conclusion and outlook with a guidance to integration of the results of this PhD thesis in **Chapter 10**.

Part 2: Environmental Sustainability Assessment in the Pharmaceutical Sector

Chapter 4 Introducing Flow as *Leitmotiv* within Process Intensification

Redrafted from:

De Soete, W., Dewulf, J. et al. (2013). "Exergetic Sustainability Assessment of Batch versus Continuous Wet Granulation based Pharmaceutical Tablet Manufacturing: a Cohesive Analysis at Three Different Levels." Green Chemistry **15**(11): 3039 - 3048.

4.1 Introduction

In the pharmaceutical industry, the world's most carbon intensive business, attention is increasingly concentrated on eco-efficient product design and product sustainability as a whole (Jiménez-González, 2000; Jiménez-González et al., 2004a; Constable et al., 2007). During the last decades, innovative chemical reactions and better performing equipment were developed in chemical synthesis for pharmaceutical manufacturing by leading companies of the American Chemical Society Green Chemistry Institute (ACS GCI) Pharmaceutical Roundtable (PR) such as GSK, Pfizer, Johnson & Johnson Group of Companies, Merck and Astrazeneca (Constable et al., 2007; Curzons et al., 2007; European Commission, 2011; Jiménez-González et al., 2011). However, in order to quantify and eventually manage sustainability of new technologies, one should measure their environmental performance. With reference to measuring methods, a life cycle approach is favoured (Chapter 1.4.2), so that displacement of environmental burden by e.g. outsourcing is avoided.

To evaluate the environmental sustainability of Active Pharmaceutical Ingredient (API) production processes, quantitative tools have recently been developed (Curzons et al., 2007; Van der Vorst et al., 2009a). Van der Vorst *et al*. (2009a) proposed a tool for assessing the integral resource consumption of individual API synthesis steps in a multipurpose API production plant, based on a cradle-to-gate approach. Wernet *et al*. (2009) developed a software tool to roughly estimate the resource use and environmental impacts of fine chemical production based on the molecular structure, circumventing the need for a process analysis. However, these tools do not give any representative indication on the environmental burden of a finished pharmaceutical Dosage Form (DF), since their focus does not go beyond the API production step (Van der Vorst et al.,

2013). Drug Product (DP) production processes though, realize the true formulation of the API in combination with multiple excipients (e.g. binders, fillers, lubricants, surfactants, etc.) in a so called DF (e.g. tablet, capsule, syringe, etc.).

Table 2: Pharmaceutical excipients and their role in formulation processes (Martinez et al., 2002).

Excipient	Role	Substances
Filler	When the amount of drug substance is insufficient to produce a tablet of practical size, a diluent is needed.	Lactose, dicalcium phosphate and pregelatinized starch
Desintegrant	In order to have a favourable release in the human body, desintegrants promote moisture penetration and dispersion of the matrix. Desintegrants overcome cohesive strengths by compression through its swelling mechanisms.	Starch, sodium starch glycolate, croscarmellose, sodium and crospovidone
Lubricant	Lubricants reduce friction at the die wall during compression, reduce adhesion and promote powder flow by reducing cohesive forces.	Silicon dioxide, magnesium and calcium stearates
Binder	The role of the binder is to facilitate the agglomeration and adhesion of particles in wet granulation. The binder also helps to hold the tablet together during compression.	Polyvinylpyrrolidone, HPMC, pregelatinized starch
Filler-Binder	Special fillers used in low-to-moderate dose drugs made by direct compression.	Microcrystalline cellulose (MCC), unmilled dicalcium phosphate
Surfactant	Increases the wetting of the powder mass or tablet matrix while enhancing the dissolution in the human body.	Sodium lauryl sulphate, sodium docusate
Antioxidant	Antioxidants provide chemical stability by inhibiting oxidation.	Ascorbyl palmitate

Coating agent	Coating agents should provide protection to the atmosphere, improve aesthetics or modify drug release.	HPMC, ethyl cellulose latexes and polymers and esters of methacrylic acid

The internal matrix of a tablet consists of the API along with its formulation excipients (Table 2 represents possible excipients according to their function), which are responsible for the tablet behaviour through the drug's life cycle (including granulation, compaction and release in the human body) (Franch-Lage et al., 2011). Disintegration, which seems to be the rate-limiting step for the dissolution of drugs, can be manipulated by choosing the optimum excipient proportions (Al-Mohizea et al., 2007). API and excipients should be homogeneously distributed, since a non-uniform distribution of API can be critical in releasing low mass proportion APIs in the human body. The latter determines the final quality of Solid Dosage Forms (SDFs). NIR hyperspectral techniques with multivariate curve resolution methods showed their use in the fast assessment of the surface distribution of API and excipients (Franch-Lage et al., 2011). Important tablet characteristics that should be considered and evaluated when changing excipients proportions or implementing a new technology are the disintegration rate, hardness, weight, dissolution and API bioavailability (Shao et al., 2007).

In the Biopharmaceutics Classification System (BCS), drugs are classified into four categories according to the compound's solubility and intestinal permeability. The first class consists of the compounds that are generally very well absorbed. These drugs have a high solubility and high permeability. The bioavailability of the second class drugs is typically dissolution-rate limited. These drugs have a low solubility but a high permeability. Class three consists of drugs with high solubility and low permeability

while class four encloses those with low solubility and low permeability, resulting in very poor oral bioavailability (Martinez et al., 2002).

One should bear in mind that the main concerns in pharmaceutical industry are safety and efficacy. Unlike in bulk food industry, small changes of drug composition for environmental reasons can impact safety and/or efficacy and become life-threatening. Another important aspect is the agility of the supply chain (lead time). Given that medication demand fluctuates, supply should be flexible and highly adaptable to possible changes in market needs (Janssen-Cilag S.P.A., 2011a).

Tablets, by far the most widely used DFs, are made in a so called tablet press through for instance direct compression. Figure 9 illustrates the working principles of a rotary press.

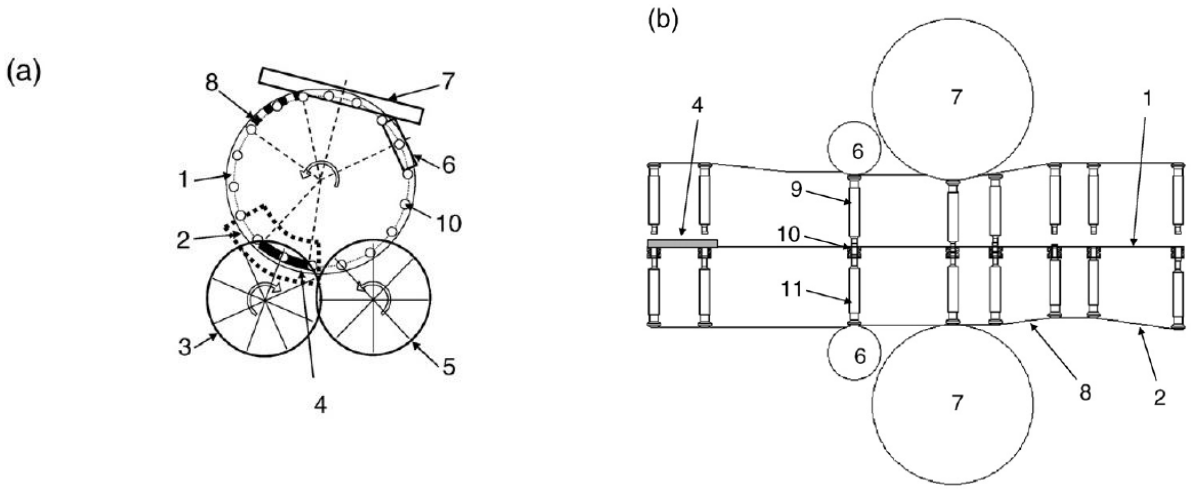

Figure 9: Rotary press production cycle. (a) top view; (b) unfolded view. (1) die table; (2) fill cam; (3) paddled feed wheel; (4) die fill area; (5) paddled metering wheel; (6) pre-compression roller; (7) main compression roller; (8) ejection cam; (9) upper punch; (10) die; (11) lower punch (Sinka et al., 2009).

However, the production of tablets mostly requires a preliminary granulation phase to enhance the flowability of the powder mix and finally to optimize tablet properties (Franch-Lage et al., 2011). Generally, a granulation solution is added to improve dissolution rates and agglomerate particles by capillary and viscous forces until more permanent bonds are formed by subsequent drying phases (wet granulation). Most established production lines are installed with batchwise operating granulators. Transition to continuous processing in the pharmaceutical industry lays far behind compared to bulk processing industries (e.g. food industry), because of high quality standards and rather small theoretical batch sizes. However, recent developments showed continuous processing to be favourable in DP production processes as well in terms of flexibility, compactness and process analytical controllability (Vervaet and Remon, 2005). Upon DP production, the dosage form should eventually be packaged, distributed and transported to the pharmacy or hospital. Figure 10 shows a basic representation of the supply chain of a pharmaceutical drug manufacturing plant, subdivided into three system boundaries. Mind that every step in the supply chain should be provided with utilities (e.g. electromechanical power, heating media, cleaning agents, etc.) and generates waste streams which are not visualized in this flow diagram for the sake of simplification.

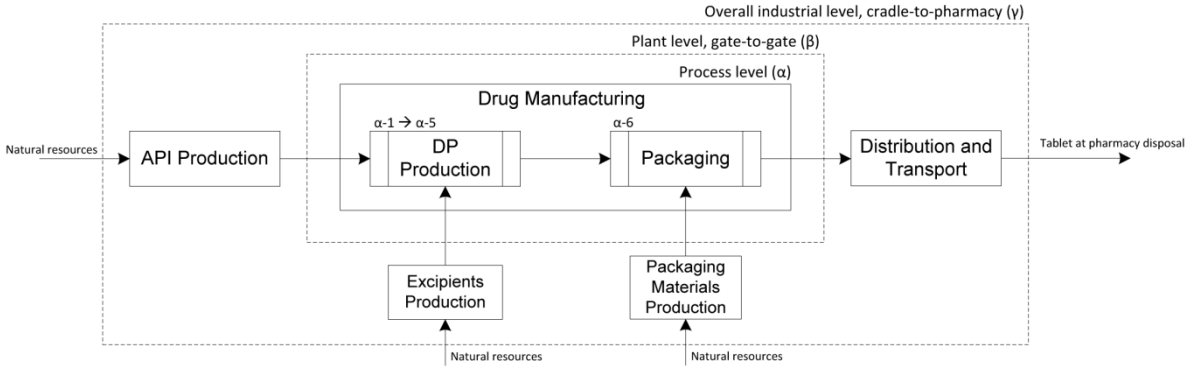

Figure 10: Basic representation of the supply chain of a pharmaceutical drug manufacturing plant, subdivided within three system boundaries: (α) process level; (β) plant level, gate-to-gate; (γ) overall industrial level, cradle-to-pharmacy. Mind that every step in the supply chain should be provided with utilities (e.g. electromechanical power, heating media, cleaning agents, etc.) and generates waste streams which are not visualized in this flow diagram.

A case study addressing environmental sustainability of all aforementioned production steps in the life cycle of pharmaceuticals would be innovative and would most likely trigger the development of new assessment tools embracing the complete life cycle of pharmaceuticals, including its End-of-Life phase.

With this chapter, the author aims at providing a state of the art exergy based environmental sustainability assessment of batch versus continuous wet granulation based tablet manufacturing at three different levels. Following a deep focus on the DP production processes itself (in this case tableting), system boundaries will be expanded towards a comprehensive cradle-to-pharmacy approach taking into account API production, DP production, packaging and distribution and transport processes. Hence, the overall impact of a pharmaceutical at the disposal of the customer is calculated for the cradle-to-pharmacy approach, together with its most sensitive parameters. Finally, the contribution of DP production processes to the total environmental burden of the pharmaceutical supply chain is illustrated. The medicine under analysis is

TRAMACET®, a high dose analgesic, produced at a pharmaceutical manufacturing plant of Janssen-Cilag SpA (part of the Janssen Group and Johnson & Johnson). Impact assessment is mainly resource based (strongly supported by e.g. A Resource-Efficient Europe – 7th Flagship Initiative under the Europe 2020 Strategy) by means of thermodynamics (European Commission, 2011). The method proved the advantage of using thermodynamic principles in pharmaceutical industrial systems, as well as in other sectors, towards a more sustainable production (Dewulf et al., 2000; Dewulf and Van Langenhove, 2002; Dincer and Rosen, 2004; Dewulf et al., 2005; Dewulf et al., 2007a; Dewulf et al., 2007b; Tsatsaronis, 2007; Dewulf et al., 2008; Van der Vorst et al., 2009b; Alvarenga et al., 2013). In order to provide a complete analysis of both ways in which industrial systems are interacting with the ecosphere (resource depletion and waste emission), the Carbon Footprint (CF) is proposed as emission based eco indicator. This way, the chapter aims both at a resource and emission based approach towards environmental sustainability of two different granulation technologies in tablet manufacturing at process level (α), plant level (β), and overall industrial level (γ).

4.2 Methodology

Methodology and results of this study are represented according to the ISO 14040 and ISO 14044 series, next to the more completely elaborated ILCD Handbook Guidelines (ISO, 2006; European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010).

4.2.1 Applied Functional Unit (FU)

The relative nature of LCA is partially due to the applied Functional Unit (FU). The primary purpose of a FU is to provide a reference to which all inputs and outputs are related. In order to yield intuitive, representative results, the FU in this study has been defined as 1 tablet of TRAMACET® which equals an approximate weight of 441 mg. One should bear in mind that this approach is in contrast to most fine chemical LCA studies (and takes us one step further to the real functionality of the medicine) that often take 1 mole or 1 kg of product as FU (Jiménez-González et al., 2004a; Van der Vorst et al., 2011).

4.2.2 Batch versus Continuous Product System

Product systems under study are the conventional batchwise and recently developed continuous production mode of TRAMACET®, a centrally acting synthetic analgesic drug (Janssen Pharmaceutica NV, 2004). The former one is located at the pharmaceutical manufacturing plant of Janssen-Cilag SpA at Latina, Italy, the latter one is located at the Product Development Centre (PDC) of GEA Pharma Systems - Collette™ in Wommelgem, Belgium. Active Pharmaceutical Ingredients (APIs) Paracetamol (Acetaminophen) and Tramadol are dosed in an $80\%_{(w/w)}$ solid dosage tablet

form. At process level (α), six main core processes can be distinguished: (α-1) dispensing; (α-2) granulation; (α-3) mixing; (α-4) compression; (α-5) coating and (α-6) packaging, of which each is subdivided into different separated subprocesses. For instance, the batchwise granulation process (α-2), making use of a top spray fluid bed granulator (Glatt®), can be described by introducing seven unit processes, while the continuous granulation process, making use of a twin screw extruder (ConsiGma™, GEA Pharma Systems – Collette™) can be characterized with only five unit processes (partly by combining agglomeration and mixing of the powder in one single step). Unlike the batch production system, in which all core processes are carried out in different and separated equipment, continuous granulation (α-2), mixing (α-3) and compression (α-4) are performed in one single continuous equipment platform (ConsiGma™), which reduces the production area. All core processes need many kinds of supporting utilities to be delivered at process level such as electricity, steam, compressed air and cleaning water. The former can be produced on-site (e.g. steam production in natural gas boilers) within the plant level (β) or can be produced somewhere in the overall industrial level (γ) (e.g. electricity retrieved from the Italian grid). In both cases, shifting from batch to continuous production does not affect the way in which utilities are produced, but mainly the quantitative amount of utilities needed. A more detailed subdivision of all processes within scope is to be found in Annex A2 and detailed flowcharts are available in Annex A3.

4.2.3 System Boundaries

In specifying the system boundaries in a cradle-to-pharmacy LCA on pharmaceuticals, one has to account for several life cycle stages: (1) API production; (2) drug product (DP) production (e.g. tablet production); (3) packaging and (4) distribution and

transport. As described above, the foreground product system is subdivided into the core process system (α level) and the on-site supporting process system, being the Janssen-Cilag SpA manufacturing plant at Latina, Italy (β level, gate-to-gate approach). Background processes are represented in the overall industrial system (γ level, cradle-to-pharmacy approach). As a result, this study provides a comprehensive resource footprint at three separated levels, creating the ability of better identifying the location of resource losses through the supply chain. The environment interacts with the α, β and γ level in supplying elementary flows (natural resources), and receiving elementary waste flows (e.g. CO_2, discharged wastewater, etc.). Product flows and intermediate flows are exchanged between α, β and γ level and should not interact directly with the environment. Figure 11 shows a representation of the three product systems and its interactions with each other and with the environment (ecosphere).

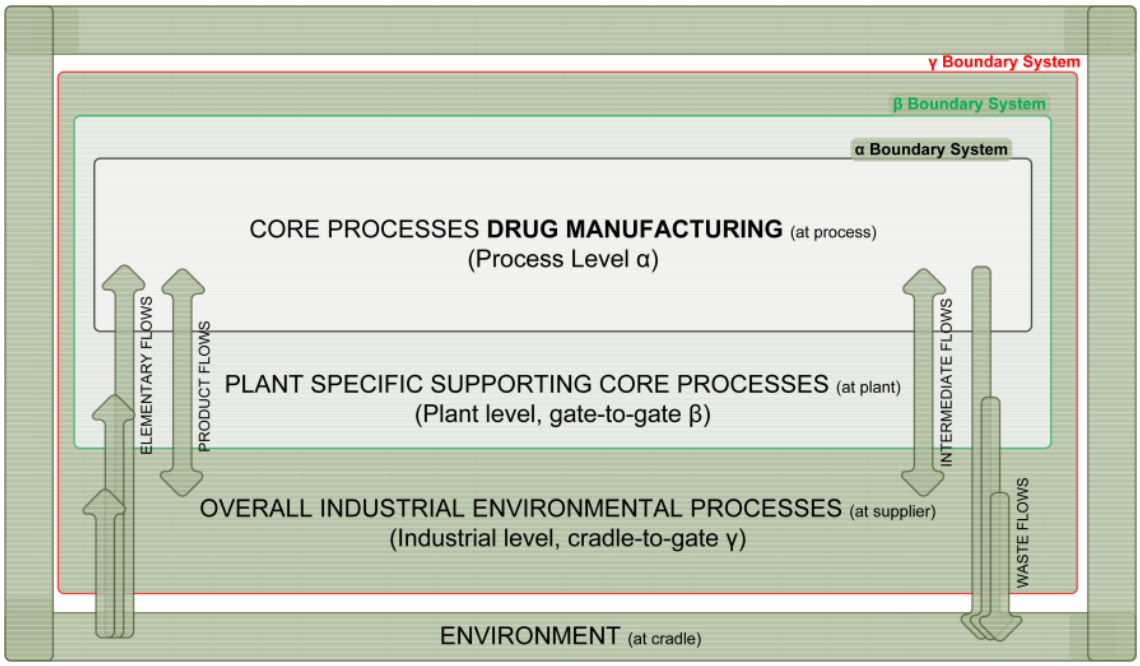

Figure 11: Three LCA system boundaries. The α level (process level) represents the six core processes. The β level (plant level) represents the on-site supporting core processes at the Janssen-Cilag SpA manufacturing plant in Latina, Italy. The overall industrial environmental processes in the technosphere define the γ level. The environment interacts with the α, β and γ level by supplying elementary flows (natural resources), and receiving elementary waste flows (e.g. CO_2, discharged wastewater, etc.). Product flows and intermediate flows are exchanged between α, β and γ level and should not interact directly with the environment.

4.2.4 Life Cycle Inventory (LCI)

The Life Cycle Inventory (LCI) clearly is the most time-consuming step in LCA (Van der Vorst et al., 2009a). At process level, most of the data were gathered at the Janssen-Cilag SpA manufacturing plant in Latina, Italy. Data on the continuous production line ConsiGma™ were retrieved from the Product Development Center (PDC) of GEA Pharma Systems – Collette™ in Wommelgem, Belgium. Industrial plant operational documents provide typical targeted data in conducting LCI (e.g. validation reports, maintenance procedures, equipment manuals, P&IDs, cleaning procedure reports, batch

reports, MSDS files and ingredient tracing documents). Table 3 gives a condensed overview of typical data sources and targeted process and plant level data for constructing an LCI. Exergetic data of background processes were extracted from ecoinvent v2.2, the Swiss database offering science-based, industrial, international LCA and Life Cycle Management (LCM) data and services (Frischknecht and Rebitzer, 2005).

Table 3: Summary of targeted LCI data on core and supporting core processes (α level & β level) and its plant specific data sources.

Documents/data sources	Targeted data
Validation reports	Mass input (α), mass yields, core processing equipment parameters (α), supporting processes operating parameters (β), equipment utility consumption, QA/QC, maintenance procedures
Equipment manuals	Nominal power consumption, equipment part analysis, equipment utility consumption, maintenance procedures
P&IDs	Equipment analysis, utility supply, product transport, identification electricity consuming moving parts, pumps, motors
Cleaning procedure reports & Standard Operating Procedures (SOPs)	Mass input for cleaning, detergent use, time of cleaning cycles
Batch reports SOPs	Process set-up times, run times, cleaning times, manual parameter settings
Materials Safety Datasheet (MSDS) files, Bill of Materials (BOM) & ingredient tracing documents	Chemical composition, supplying companies, production processes, supplier location, transport categories
Expert interviews	Detailed information on specific processes

4.2.5 Impact Categories

At α and β level, the impact assessment is performed through Exergy Analysis (EA) which mirrors the resource consumption and resource consumption efficiency of a certain process, product or service, based on the principles of thermodynamics (Apaiah et al., 2006; Hammond, 2007) (Chapter 1.4.1). This approach at different levels allows one to identify and locate exergy or resource quality losses at the plant. The impact assessment method used at γ level is the Cumulative Exergy Extracted from the Natural Environment (CEENE) (Dewulf et al., 2007a). Compared to the Cumulative Exergy Demand (CExD), proposed by Bösch *et al*. (2006), this method can be considered as an extended resource footprint since it covers eight impact subcategories of resource use: (1) fossil resources; (2) metal ores; (3) nuclear energy; (4) land resources including biomass production; (5) renewable resources other than biomass; (6) minerals; (7) atmospheric resources and (8) water resources (Bösch et al., 2006; De Meester et al., 2006; Dewulf et al., 2007a). Coupling this resource based approach with an emission based approach increases the relevance of the indication to judge the total environmental burden of a given product. The Carbon Footprint (CF), expressed in kg CO_2-eq, showed its relevance as emission based indicator in energy intensive industries. The latter is approached as the equivalent total amount of CO_2 and other greenhouse gases (GHG) emitted over the full cradle-to-pharmacy approach of a pharmaceutical (Wiedmann and Minx, 2007).

4.2.6 Calculations

In calculating the impact indicators, exergy content of material and energetic resources were computed based on the reference conditions of Morris and Szargut (1986) (Morris and Szargut, 1986). For solid chemical species, the most stable state of the pure elements

at T_0 = 298.15 K and p_0 = 101.325 kPa were employed. Whenever possible, for organic chemicals, the group contribution method was used (Szargut et al., 1988). Table 3 illustrates the latter with an example (Acetaminophen, API).

Table 3 Example of Szargut's group contribution method for organic chemicals: Acetaminophen, API.

Group	Amount (#)	$ex_j^{\circ CH}$ (kJ_{ex}/mol)	Total (kJ_{ex}/mol)
CH_3-	1	752.03	752.03
NH--	1	195.56	195.56
C-- (arom)	2	436.45	872.90
CO-	1	277.76	277.76
HC- (arom)	4	547.15	2,188.60
OH-	1	-51.34	-51.34

Chemical exergy of Acetaminophen: 4 235.51 kJ_{ex}/mol

For salt formation with organic molecules (e.g. sodium starch glycolate), the group contribution method was combined with the Gibbs free energy of the salt formation and crystallization processes, following upon the dissolution of the reference compound (e.g. $Na(OH)_s$). The exergy content of packaging materials were found in literature (Gong, 2005). The exergy content of PVC and detergent were calculated with the group contribution method. Aluminum foil exergy content was calculated assuming a composition of 95% Al and 5% Al_2O_3 (Morris and Szargut, 1986).

When using liquid mixtures or aqueous solutions, a term for molar mixing exergy was added up to the total chemical exergy content of the substance:

$$ex_{mix} = R \times T_0 \times \sum_i x_i \times \ln(\gamma_i \times x_i) \qquad (22)$$

with R the universal gas constant, T_0 the temperature of the reference state and x_i and γ_i the molar fraction and activity coefficient of compound i respectively (Szargut et al.,

2005). Note that mixing exergy will add a negative term to the total exergy of the mixture, since work is necessary to separate mixture compounds.

Morris and Szargut (1986) refer to the reference compounds for the nine gaseous elements C, H, O, N, Ar, Ne, He, Kr, Xe as the gaseous compounds of atmospheric air at T_0 = 298.15 K and p_0 = 101.325 kPa, assuming ideal gas behaviour. When temperature or pressure differences occur, the physical exergy of air changes according to the following formula:

$$ex^{PH} = \left| c_p \times \left[(T - T_0) - T_0 \times \ln \frac{T}{T_0} \right] \right| + \left| R \times T_0 \times \ln \frac{p}{p_0} \right| \quad (23)$$

in which c_p is the isobaric specific heat capacity of air, R the universal gas constant and T_0 and p_0 the temperature and pressure of the reference state respectively (Cornelissen and Hirs, 2002). T and p are the respective temperature and pressure of the airstream under study. Note that exergy calculations were explained in detail in Chapter 1.3.7.

As for purified water, condensed water, superheated water and steam, the chemical exergy is calculated based on the molarity of the reference species in seawater (Morris and Szargut, 1986). Physical exergy of water and steam was calculated using the following established formula:

$$ex^{PH} = (H - H_0) - T_0 \times (S - S_0) \quad (24)$$

in which H_0, T_0, S_0 are the enthalpy, the temperature and the entropy of the water at its reference state (T_0 = 298.15 K and p_0 = 101.325 kPa) respectively (Szargut et al., 2005). H and S are the respective enthalpy and entropy of the stream under consideration.

The exergy content of natural gas was calculated using the gas composition of the supplier and the compound's Gibbs free energy of formation. Note that this could easily be calculated as well with the empirical formula for fuels and biomass:

$$ex_{ch} = \beta \times LHV \tag{25}$$

with LHV the Lower Heating Value of the fuel and β the exergy to energy ratio, depending on the atomic composition of the substance (Szargut et al., 1988). The energy content in 1 kJ of electricity can be made available for one hundred per cent in work delivery, so its exergy content is by definition 1 kJ_{ex}.

To calculate the life cycle impact data, the CEENE method was coupled with the ecoinvent v2.2 life cycle database. An X factor allows the calculation of the former for the 184 classified resource reference flows, after Dewulf *et al*. (2007):

$$CEENE_j = \sum_{i=1}^{184} (X_i \times a_{ij}) \tag{26}$$

in which $CEENE_j$ (MJ_{ex}) is the total cumulative exergy extracted from the natural environment for a product or service j, X_i the X factor of the i^{th} reference flow (MJ_{ex} per functional unit) and a_{ij} the cumulative amount of the reference flow expressed in its functional unit (Dewulf et al., 2007a).

The IPCC GWP 100a Carbon Footprint (CF) was calculated based on the emission factors of the ecoinvent reference flows.

4.2.7 Allocation Procedures

While in bulk chemical processes, by-product formation is often unavoidable and sometimes even profitable, in pharmaceutical tablet manufacturing process allocation is rather limited. Most of chemical feedstock resources at process level will contribute to tablet formation only. Nevertheless, allocation should be considered in assigning process plant utilities to the different unit processes at process level (α). The latter is based upon physical causalities – in this case exergy - as is encouraged in the ILCD Handbook (European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010).

4.2.8 Assumptions and Limitations

Taking into account the production setup at process level (α), few assumptions had to be made, mostly due to lack of data or the introduction of justified simplifications to avoid redundant model complexity. Generally, it should be stressed that no cooling water consumption is taken into account because of lack of consistent plant data and the rather modest contribution to total resource extraction (Van der Vorst et al., 2009a). Cooling water is used for dehumidifying drying air and for cooling the granulator barrel. For cleaning of the ConsiGma™, the current cleaning procedures of the batch Tramacet® production were adopted because cleaning is highly relative to the specific powder characteristics. However, this is likely to result in an overestimation of resource consumption due to cleaning of the continuous production line since less material should be cleaned and Cleaning in Place (CIP) can be installed. For the production of tablet excipients, the most representative ecoinvent flows were used. For very specific materials (e.g. detergents), a mixture of flows was implemented according to the

composition of the chemicals. CEENE values of APIs were obtained from previous studies (Van der Vorst et al., 2009a).

4.3 Results and Discussion

Through the results and discussion section, resource extraction at process (α) and plant level (β) will be represented by means of five functional categories: (1) chemicals; (2) heating media; (3) electromechanical power; (4) cleaning agents and their disposal and (5) compressed air. At overall industrial level (γ), additional subdivision of resource extraction will be provided through the CEENE impact categories.

4.3.1 Process Level (α)

Out of the overall mass and energy balances at process level, thermodynamic analysis resulted in consistent exergy balances over each unit operation within the pharmaceutical production chain of TRAMACET®. Focusing on granulation, the heart of pharmaceutical tablet manufacturing, Figure 12a illustrates the resource consumption within the batchwise granulation phase (α-2), expressed in kJ_{ex}/tablet. The high contribution of chemicals to the total resource extraction in granulation is due to the Active Pharmaceutical Ingredient (API) and excipients. The contribution to heating in the spraying and drying phase is attributable to steam consumption for dry air heating. Likewise, electricity is consumed mainly in the spraying and drying phase. Cleaning of the Glatt® top spray fluid bed granulator is performed at the end of the granulation process. Figure 12b shows that continuous granulation of Tramacet® within the ConsiGma™ consumes up to 29.0% less resources compared to batch granulation.

While the load of API and excipients remains more or less the same (apart from slightly different mass yields), a reduction of 72.0% utility consumption can be deduced from Figure 12b. The latter is especially caused by a more efficient heating in the granulator barrel and reduced power consumption of the granulator drive. Expanding the focus to the overall process level reveals the high contribution of packaging materials to the total resource consumption (up to 54.0%), caused by the high relative mass of packaging materials per packed tablet (1.81 g/tablet). For the TRAMACET® case however, only 10 tablets were packaged per folding box (primary packaging), whereas approximately 25 tablets per folding box can be assumed as default value in pharmaceutical manufacturing (Janssen-Cilag S.P.A., 2011b).

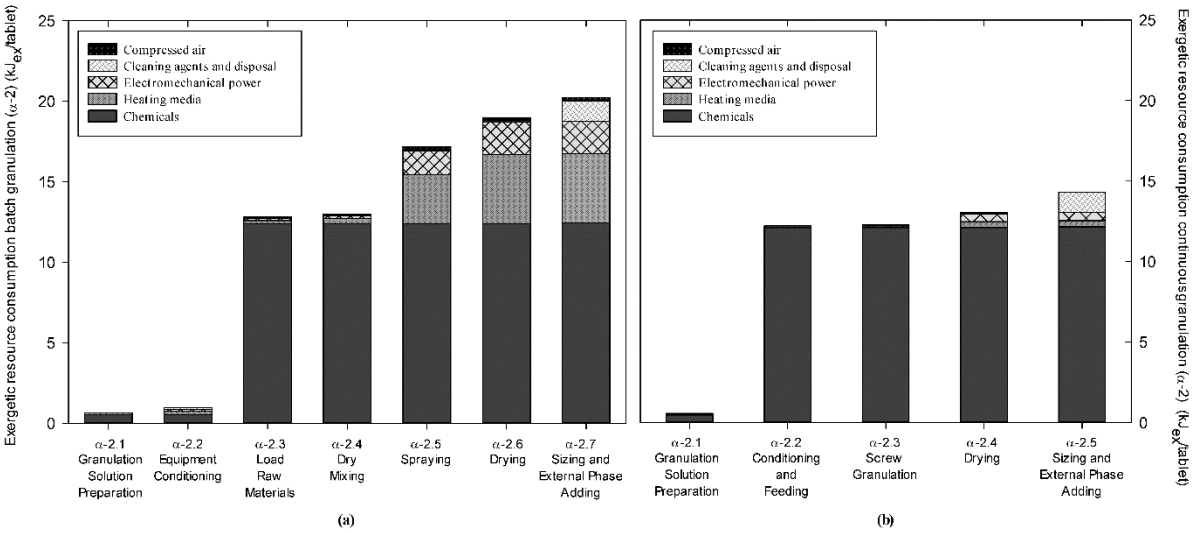

Figure 12: (a) Cumulative resource consumption expressed in kJ_{ex}/tablet within the batchwise granulation phase (α-2). The high exergetic value of chemicals is incorporated mainly in API and excipients. The contribution to heating media in spraying and drying media is due to steam consumption for dry air heating. Likewise, electricity is consumed mainly in spraying and drying phases. Resources for cleaning agents and their disposal are allocated to the final phase, in which cleaning is performed; (b) Cumulative resource consumption expressed in kJ_{ex}/tablet within the continuous granulation phase (α-2).

In shifting from batch to continuous manufacturing, a total resource consumption reduction of 10.2% (65.6 to 58.9 kJ_{ex}/tablet) was obtained, taking into account all

resource inputs at process level. However, since more or less the same amounts of API, excipients and packaging materials were needed in both batch and continuous manufacturing setups, excluding this so-called transiting exergy showed a total utility consumption reduction of 34.0% (Figure 13).

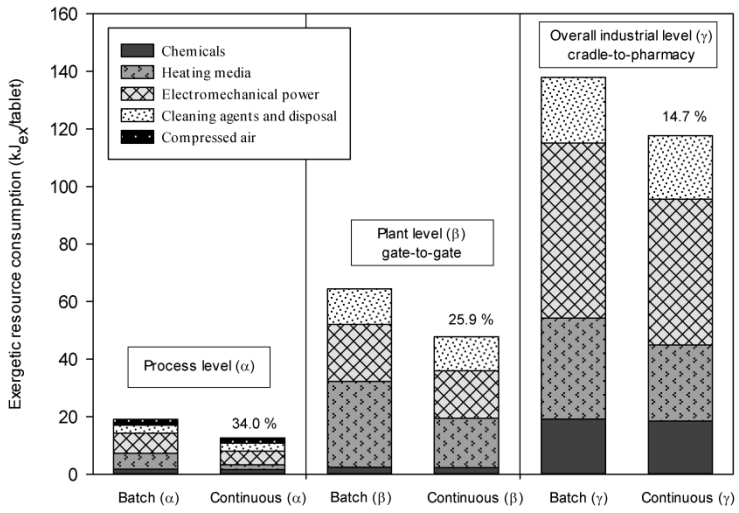

Figure 13: Cumulative exergetic resource consumption at process level (α), plant level (β) and overall industrial environmental level (γ), excluding transiting exergy in API, excipients and packaging materials. Contribution to resource consumption is expressed in functional categories (in kJ_{ex}/tablet) for batch versus continuous drug product (DP) production processes.

Results of the process efficiency analysis are shown in Table 4. η_1 and η_2 represent the simple and rational efficiencies respectively expressed by the ratio of the sum of exergy contents of product and waste and the exergetic input components on the one hand, and the ratio of product exergy and exergy content of input components on the other hand. A third type of efficiency η_3 was introduced to better reflect the utilisation efficiency of process utilities (e.g. steam, hot water consumption, compressed air, etc.). In this definition, transiting exergy in API, excipients and packaging materials was subtracted from both numerator and denominator. The irreversibility generation provided in Table 4 is the amount of exergy lost through the process due to process inefficiencies. This

amount of exergy can never be recovered as such, being a direct consequence of the second law of thermodynamics (law of entropy) (Dewulf et al., 2000). It is to be noticed that less exergy is irreversibly lost following the implementation of the continuous production line (up to 43.0% reduction). For process efficiencies and irreversibility generation of all core processes (e.g. dispensing, granulation, mixing, etc.), the reader is referred to Annex A4.

Table 4: Summary of batch versus continuous wet granulation based tablet manufacturing resource efficiency analysis and irreversibility generation at process level (α).

	Batch	Continuous
Simple efficiency (η_1)	78.6%	86.5%
Rational efficiency (η_2)	71.7%	80.0%
Utility efficiency (η_3)	24.4%	32.8%
Irreversibility generation	14.0 kJ/tablet	8.0 kJ/tablet

4.3.2 Plant Level (β)

At plant level, the contribution of utilities to total resource consumption is higher since most process utilities are produced on-site (e.g. steam from natural gas boiler), whereas at process level the contribution of packaging materials seems to be dominant. In shifting from batch to continuous manufacturing, a total resource consumption reduction of 15.2% (111 to 94.0 kJ_{ex}/tablet) was calculated, taking into account all resource inputs at plant level. Excluding transiting exergy showed a reduction of 25.9% (64.6 to 47.7 kJ_{ex}/tablet, see Figure 13). In the existing batchwise configuration of the pharmaceutical manufacturing of TRAMACET® an input of 111 kJ_{ex} results in a waste generation of 18.3 kJ_{ex} per tablet (47.0 kJ_{ex}) at the manufacturing plant of Janssen-Cilag SpA. Bearing in mind the total input at the process level in batch setup (65.6 kJ_{ex}), one would expect

an irreversibility generation of 45.6 kJ_{ex} at the plant. 57.6% of total resource input at the plant is lost, mainly by heat losses in steam generation, pressure losses in reverse osmosis, electricity inputs and wastewater disposal. 41.1% is irreversibly lost, while 16.5% is considered as waste that can be recovered in some way (e.g. wastewater, exhaust air rest heat). Losses at plant level could be reduced by 18.0% if wastewater is valorised or recycled in some way for cleaning or cooling purposes, while up to 8.0% of all plant losses could be avoided by recycling the rest heat in exhaust air.

Table 5: Summary of batch versus continuous wet granulation based tablet manufacturing resource efficiency analysis and irreversibility generation at plant level (β).

	Batch	**Continuous**
Simple efficiency (η_1)	58.9%	67.4%
Rational efficiency (η_2)	42.4%	49.9%
Utility efficiency (η_3)	28.6%	34.9%
Irreversibility generation	45.6 kJ/tablet	30.7 kJ/tablet

4.3.3 Overall Industrial Level (γ)

Some of the utilities (e.g. electricity from the Italian grid) or material feedstock resources (e.g. API, excipients, packaging materials) are produced elsewhere in the overall industrial environment. This γ level approach comprises all production steps from cradle-to-pharmacy. The CEENE value of one tablet of TRAMACET® at pharmacy gate numbers up to 2.3 MJ_{ex}/tablet in the batch production setup. By introducing the ConsiGma™ as a continuous production line, the primary results showed a reduction of only 2.2% (2.2 MJ_{ex}/tablet) taking into account all resources.

Since TRAMACET® is a high dose drug (API percentage more than 80.0%(w/w)), it is conceivable that API synthesis steps (which are identical for both batch and continuous drug production phases) will to some extent neutralize the efforts made towards greener drug product (DP) production processes. Focusing on the DP production step only by excluding transiting exergy revealed a 14.7% reduction of cumulative resource consumption (138 to 118 kJ_{ex}/tablet) at the cradle-to-pharmacy level (γ), as shown in Figure 13. Overall, pharmaceutical manufacturing of TRAMACET® can be associated with a Coefficient of Performance (COP) of 2.1%, which is a low ratio, typical for the complex pharmaceutical industry (Van der Vorst et al., 2011).

Expressed in functional categories, cumulative resource extraction at γ level proved to be dominated by the chemical category (due to the API production step), while at process and plant level, resource consumption was dominated by the use of packaging materials and utilities respectively. Excluding transiting exergy in API, excipients and packaging materials, Figure 13 visualizes the high contribution of the electromechanical power and heating media categories. Out of the rather high increase of the contribution of heating media at plant level compared to the process level, one can identify on-site steam production. As for electricity, an increased contribution is noticed at overall industrial level, retrieved from the Italian electricity grid (off-site production). Approaching environmental impact of DP production of Tramacet® from a resource point of view at the cradle, a resource footprint of the tablet drug under analysis is disclosed. 65% of resource extraction from the natural environment is due to fossil resource depletion, 15% to water resources, 15% to land occupation and biomass production and approximately 5% to nuclear energy and renewable resources other than biomass (Figure 14). By implementing the continuous production line of GEA Pharma Systems – Collette™, the fossil resource contribution to total resource extraction proved

to decrease predominantly due to a lower utility consumption. Overall, comparing this resource footprint of DP production processes with the API synthesis steps raises the awareness of an even higher contribution of fossil resource extraction for API synthesis (up to 75%), which confirms previous findings (Van der Vorst et al., 2009a; Van der Vorst et al., 2011). As for DP production processes, the substantial contribution of land occupation and biomass production (15%), which used to be barely noticed in API synthesis, proved to be caused by the use of starch based excipients (e.g. filler or binding material) and the application of paper and cardboard as mainly cellulose based packaging materials. As for distribution and transport processes, resource extraction could almost entirely be assigned to fossil resource consumption (Figure 14).

As already has been stated in Chapter 4.1, a resource based approach towards environmental sustainability creates the possibility of acting proactively, while focusing on emissions might eventually favour end of pipe solutions. However, a combined impact assessment is the preferred way to really understand both ways in which nature is interacting with our industrial systems. From an emission point of view, a Carbon Footprint (CF) reduction of 2.0% (0.22 to 0.21 kg CO_2-eq/tablet) was obtained at γ level in shifting from batch to continuous manufacturing of TRAMACET®. Focusing on DP production revealed a CF reduction of 16.2%. This reduction in GHG emissions showed to be strongly correlated with the fossil resource part reduction of total resource extraction, as earlier stated by Huijbregts et al. (2006), which evidences a resource oriented focus to act proactively (Huijbregts et al., 2006). An average GHG emission of 0.215 kg CO_2-eq/tablet, as obtained within this case study, confirms earlier assumptions made by e.g. England's NHS Sustainable Development Unit highlighting the remarkably high contribution of pharmaceuticals to the NHS England CF (up to 22%) (NHS Sustainable Development Unit, 2012). However, little knowledge was acquired

about the importance of different pharmaceutical production steps contributing to the total environmental burden of these pharmaceuticals.

4.3.4 Impact of Drug Product (DP) Production Processes through the Pharmaceutical Supply Chain

Through the preceding paragraphs, the reader has sensed the importance of the API production processes in the overall industrial environmental system approach for the TRAMACET® case study (see Figure 14). In order to fairly represent changes in shifting from batch to continuous DP production processes, the concept of excluding transiting exergy in APIs was introduced. However, more general results were obtained by performing short, local sensitivity analysis that disclosed an increased relevance of the impact of DP production processes for low dose drugs (e.g. sedative drugs or hormones). The API concentration seemed to be the parameter with highest sensitivity towards environmental burden from a resource point of view. The amount of tablets packaged per folding box (primary packaging), proved to be the second most sensitive parameter. To illustrate this sensitivity, a typical low dose tablet formulation of 10 mg API, LIPITOR® (Pfizer's most successful blockbuster drug), was modelled assuming the same batchwise DP production process as TRAMACET®. The results as visualized in Figure 14 indicate the importance of the DP production processes and packaging processes. Further on, since the CEENE of excipient materials is lower than that of the API, total resource extraction for the estimated LIPITOR® drug proved to be significantly lower than that of TRAMACET® (0.63 MJ_{ex}/tablet versus 2.3 MJ_{ex}/tablet). In the end, identification of the former sensitive parameters contributes to the possibility of designing sustainable next generation pharmaceuticals, which is of highest importance in pharmaceutical research and development towards innovative process intensification.

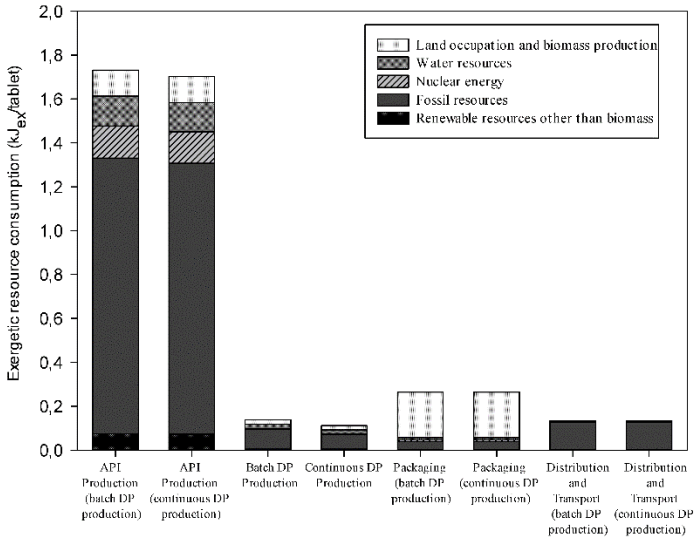

Figure 14: Contribution in total resource extraction (kJ_{ex}/tablet) of the different stages in the pharmaceutical production chain of high dose drug TRAMACET®, taking into account all upstream and downstream related processes to the production. Note that, for low dose drugs (e.g. sedative drugs or hormones), the contribution of the API chemical synthesis will decrease. The decrease in API production will be somewhat neutralized by the addition of more binder and filling materials (excipients). Since the CEENE of excipient materials is lower than that of the API, it is to be expected that the total CEENE of the tablet will decrease as API concentration decreases in the relevant drug under analysis.

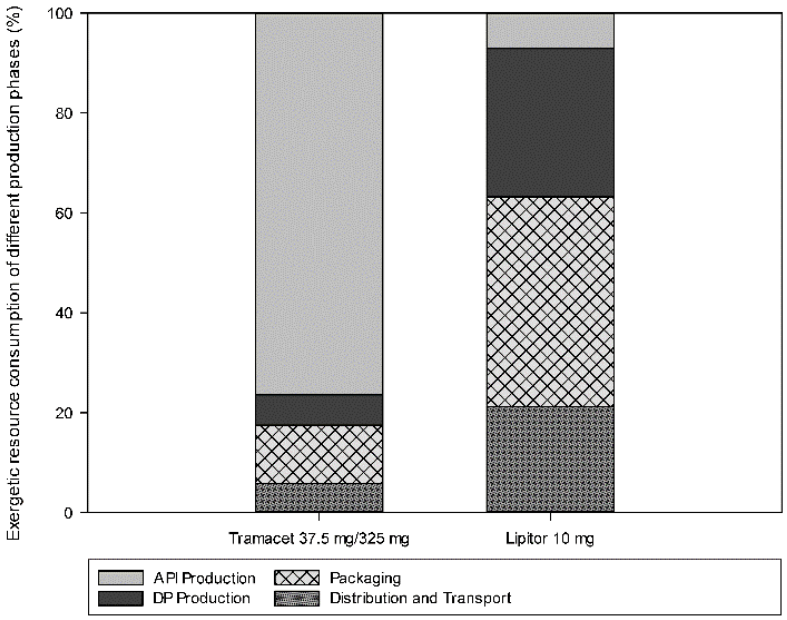

Figure 15: Exergetic resource extraction contribution of different production phases of TRAMACET® (high dose drug) versus a typical low dose tablet formulation of 10 mg API (LIPITOR®), presuming the same production process as the batchwise TRAMACET® production. Mind the importance of the drug product (DP) production and packaging phase in the overall industrial environmental system approach for the low dose drug.

4.4 Conclusion

In the light of accomplishing a more sustainable pharmaceutical production, more specifically reducing its resource consumption, a comparative exergy based sustainability assessment of batch versus continuous wet granulation based tablet manufacturing is proposed for the TRAMACET® case (high dose drug). The potential implementation of the continuous ConsiGma™ production line (GEA Pharma Systems – Collette™) at the pharmaceutical manufacturing plant of Janssen-Cilag SpA at Latina, Italy would mean a significant step forward towards green engineering and green pharmaceutical manufacturing. Recent developments towards in-line blending and coating can even further reduce the environmental burden of Drug Product (DP) production processes. Based on Exergy Analysis (EA) and Exergetic Life Cycle Assessment (ELCA), a resource consumption reduction of 10.2%, 15.2% and 2.2% at process (α), plant (β) and overall industrial level (γ) respectively was obtained. Focusing on DP production processes by excluding transiting exergy in API, excipients and packaging materials resulted in a reduction of 34.0%, 25.9% and 14.7% at the respective boundary systems. From an emission point of view, a Carbon Footprint (CF) reduction of 4 g CO_2-eq/tablet was obtained.

The study stresses the significantly high contribution of API chemical synthesis steps to the total environmental burden for high dose drugs such as TRAMACET®. However, the environmental impact of DP production processes should not be underestimated, as the latter can become predominant for low dose drugs (e.g. sedative drugs, hormones, etc.). Furthermore, attention should be paid to the amount of tablets packaged per folding box, since raising this parameter proved to be a rather straightforward way of reducing the environmental impact per tablet. Nevertheless, one should bear in mind

that results of this case study cannot not just be generalised. Eventually, in order to fully understand the various contributions of the different steps in the pharmaceutical supply chain to the total environmental burden, more cases of different kinds of dosage forms (e.g. liquids, semi-liquids, gases) should be investigated, leading to the establishment of a more generic model comprising all steps in pharmaceutical manufacturing. On the long term, one should strive for interfaced, modular models enabling user friendly scenario analysis by changing operational parameters, by simply dragging and dropping new equipment, or by implementing new production lines into an existing model to ease the accessibility for decision or policy makers.

Chapter 5
Small Molecules versus Biologicals: The Environmental Resource Footprint

Redrafted from:

De Soete, W., Rentería Gámiz, A. G., et al. (2016). "Small Molecules versus Biologicals: The Environmental Resource Footprint." Nature Biotechnology **to be submitted**.

5.1 Introduction

Since their introduction on the market biologicals or Large Molecules (LMs) were predicted to be the forthcoming blockbusters because of their unique characteristics in targeting before often undruggable diseases (Sindelar, 2013; Tsomaia, 2015). Especially within the field of Monoclonal Antibodies (MABs) the biological origin of the cell bank, fermentation processes, their typical parenteral administration and the development of new drug delivery devices implied new challenges in terms of technology, safety, efficacy, regulations and sustainability (Sindelar, 2013). Compared to the chemically produced Small Molecules (SMs), one had to deal with a completely new field of medicines. Most of those new aspects are controlled by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, when it comes to – in particular environmental – sustainability, very little is known about these new medicines compared to SM Active Pharmaceutical Ingredients (APIs) (Jiménez-González and Woodley, 2010). How do LMs behave in terms of environmental resource footprinting? How 'bio' are biological processes? What is the effect of long acting LMs on medicine consumption during treatment? Are we indeed consuming less fossil resources compared to the very energy intensive SM synthesis routes with typically a contribution of about 80% of the resource footprint due to fossil resources (Wernet et al., 2010; Van der Vorst et al., 2011; De Soete et al., 2013; De Soete et al., 2014a; De Soete et al., 2014b)? The types of data needed to perform an environmental sustainability assessment are often not (yet) well documented in LM manufacturing which makes it very difficult and time-consuming to give proper answers to the questions above (Jiménez-González and Woodley, 2010).

This chapter proposes the first resource based environmental sustainability assessment of the production of LMs versus SMs. The pharmaceutical products within scope are STELARA® 45mg, SIMPONI® 50mg, PREZISTA® 800mg and TRAMACET® 400mg of which the first two are LMs and the last two SMs. The LMs are MABs targeting auto-immune diseases such as psoriasis plaque. For patients with these types of auto-immune illnesses, such long-acting-release products (LARs) not only improve lifestyle by minimizing exposure to the needle, but also generally improve patient outcomes by improving patient compliance and reduce peak-and-valley blood levels (through the characteristics of a long acting platform) (Andreakos et al., 2002; Schwendeman et al., 2014). PREZISTA® is known as a protease inhibitor (SM) to treat the Human Immunodeficiency Virus (HIV) whereas TRAMACET® is an opioid painkiller. Figure 16 graphically represents the scope of this research chapter; a cradle-to-gate analysis of LMs versus SMs. In order to answer the above formulated questions, the authors defined three objectives: (1) to calculate the relative contributions to the resource footprint (composition); (2) to conduct absolute resource consumption analysis at product level (per dosage form) and (3) to conduct absolute resource consumption analyses at the treatment level (per Defined Daly Dose, DDD).

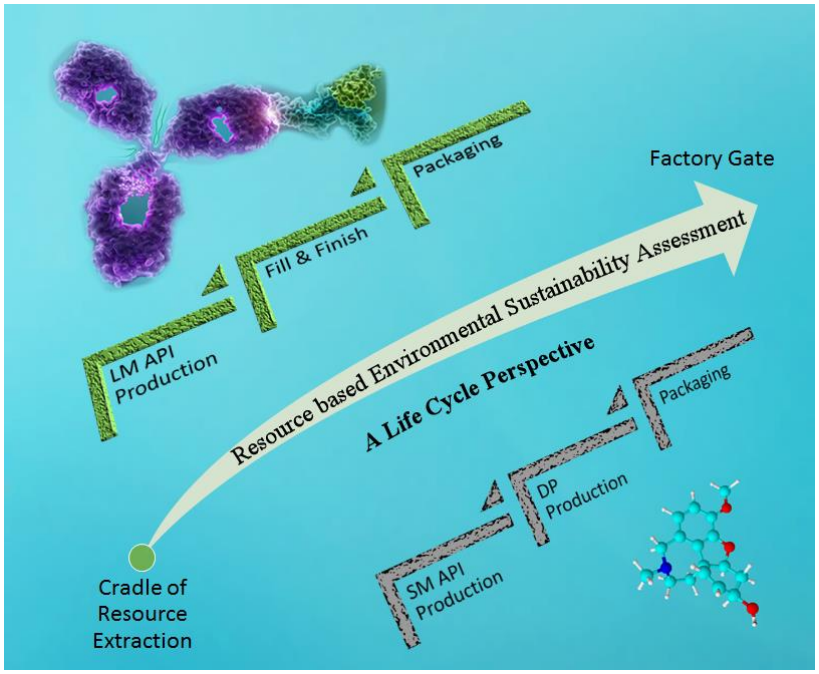

Figure 16: Representation of the scope of this chapter: a cradle-to-gate analysis of the production of Large Molecules (LMs) versus Small Molecules (SMs). The production stages included are Active Pharmaceutical Ingredient (API) production, Fill & Finish (LM), Drug Product (DP) production (SM) and Packaging. The LM visualized on top is a graph designed by Johnson & Johnson and adopted from the information portal on STELARA® (Janssen Biotech Inc., 2016).

5.2 Methodology

Methodology and results of this study are represented according to the ISO 14040 and ISO 14044 series, next to the more completely elaborated ILCD Handbook Guidelines (ISO, 2006; European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010).

5.2.1 Applied Functional Unit (FU)

For the relative contribution analysis, 1 finished (packed) dosage form is used as a Functional Unit (FU). The same is valid for the absolute comparisons at product level. One should make the comment here that it is by no means the intention of the author to make absolute one-to-one comparisons. The idea is to trace back the general trends in technology platforms (in this case long acting platforms of MABs versus immediate release Small Molecules both tackling – to some extent – different type of immune deficiency disorders). To be able to make more fair absolute comparisons, the Defined Daily Dose (DDD) is used as a metric at the treatment level. According to the WHO, the DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO Collaborating Centre for Drug Statistics Methodology, 2015). This comparative analysis will only be done for those three medicines targeting immune diseases.

5.2.2 System Boundaries

Related to the Large Molecules (LMs) under analysis, this Life Cycle Assessment (LCA) comprises a cradle-to-gate approach accounting for the following life cycle stages: (1) Biologic Active Pharmaceutical Ingredient (API) LM Manufacturing (upstream in Leiden, The Netherlands, and downstream purification in Cork, Ireland; (2) Fill and Finish of the syringes, safety device and needle cap in Schaffhausen, Switzerland; (3) Packaging in Schaffhausen, Switzerland and (4) logistic transport to the European Distribution Centre (EDC), La Louvière, Belgium, in case of STELARA™ and transoceanic shipment to Indianapolis, United States, in case of SIMPONI™.

For the Small Molecules under analyses, equal system boundaries were drawn, being cradle-to-gate, with of course different unit processes: (1) Chemical synthesis of the API SM at Grünenthal Group, Germany, for TRAMACET® and Cork, Ireland, for PREZISTA™; (2) Drug Product Production (in this case tabletting through wet granulation and rotary compression) and (3) Blister Packaging in Gurabo, Puerto Rico, for PREZISTA™ and Latina, Italy for TRAMACET®. For both cases, distribution to the EDC in La Louvière, Belgium was modelled.

5.2.3 Life Cycle Inventory (LCI)

At process level, most of the data were gathered at the respective sites as mentioned above, except for some proxy data that was used for the Gurabo site. As was already illustrated in Chapter 4.2.4, industrial plant operational documents provide typical targeted data in conducting LCI, especially in the field of SMs (e.g. validation reports, maintenance procedures, equipment manuals, P&IDs, cleaning procedure reports, batch reports, MSDS files and ingredient tracing documents). Table 3 on page 67 gives a good protocol with typical data sources and targeted process and plant level data for constructing an LCI for SMs. For LCA data, ecoinvent 2.2 was used. Because biological processes are much more difficult to control and the variability on the process data is generally higher than in the case of SMs, the table for data inventory looks somewhat different for the LMs and is given below.

Table 6: Summary of targeted LCI data on core and supporting core processes (α level & β level) and its plant specific data sources at the respective plants mentioned above (in case of LMs STELARA™ and SIMPONI™).

Documents/data sources	Targeted data
Validation reports	Mass input (α), mass yields, core processing equipment parameters (α), supporting processes operating parameters (β), equipment utility consumption
P&IDs	Equipment analysis, utility supply, product transport, identification electricity consuming moving parts, pumps, motors
Batch reports SOPs	Process set-up times, run times, cleaning times, manual parameter settings
Materials Safety Datasheet (MSDS) files, Bill of Materials (BOM) & ingredient tracing documents	Chemical composition, supplying companies, production processes, supplier location, transport categories
Expert interviews	Detailed information on specific processes, maintenance procedures, cleaning procedures

5.2.4 Impact Categories

As for this chapter, the resource footprint of the four medicines under analysis was calculated using a cradle-to-gate Life Cycle Assessment (LCA). The Cumulative Exergy Extracted from the Natural Environment (CEENE) was used as impact assessment methodology, yielding a resource footprint subdivided in eight subcategories: (1) fossil fuels; (2) metal ores; (3) nuclear energy; (4) land resources and biotic renewables; (5) renewable resources other than biomass; (6) minerals; (7) atmospheric resources and (8)

water resources (Bösch et al., 2006; De Meester et al., 2006; Dewulf et al., 2007a). For the sake of clarity, the results will be expressed in kg of crude oil exergy equivalents.

5.2.5 Allocation Procedures

Depending on the types of data that were available and accessible for the different medicines or platforms under analysis, allocation is to be performed to a certain extent. In the absence of bottom-up up engineering data, top down building or plant consumption data was allocated to the medicine under analysis. The latter is based upon physical causalities – in this case exergy - as is encouraged in the ILCD Handbook (European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010). Obviously the choice for bottom-up or top-down building level approach for data inventory will influence the uncertainty on the results, as will the modelling choices and parameters used.

5.2.6 Assumptions and Limitations

Coming to assumption and limitations that should be carefully addressed in the interpretation of the results, it is important to state that it is not the intention to make absolute comparisons of medicines, but rather characterise the resource consumption in producing MABs through the long acting parenterals platform and compare it to the most used dosing forms of Small Molecules, being blistered tablets. It is a first exploration of technology platforms of Large Molecule production.

5.3 Results and Discussion

The relative contributions to the resource footprint of the four medicines under analysis is shown in the upper part of Figure 17. The contribution of fossil resources amounts up to 69.3% and 64.8% of the resource footprint for the production of PREZISTA® and TRAMACET® respectively (both finished as blistered tablets). This high contribution is mainly due to the use of solvents and other types of chemicals, electricity consumption for the production of utilities, etc. The water footprint (5.7 and 7.7% respectively) is to be explained by the production and use of Process Reaction Water (PRW) and cleaning media. Land resources and biotic renewables (biomass production, up to 17.7%) are due to the use of starch based excipients but not the least to the paper, cardboard and wood used in the different packaging stages. Last, nuclear (4.6 and 7.4%) and abiotic renewable (2.8 and 3.8%) resources are used in the production of the applied electricity mix (and will as a result vary significantly from one production site to another). It was to be expected that the production of biologicals (in this case MABs)

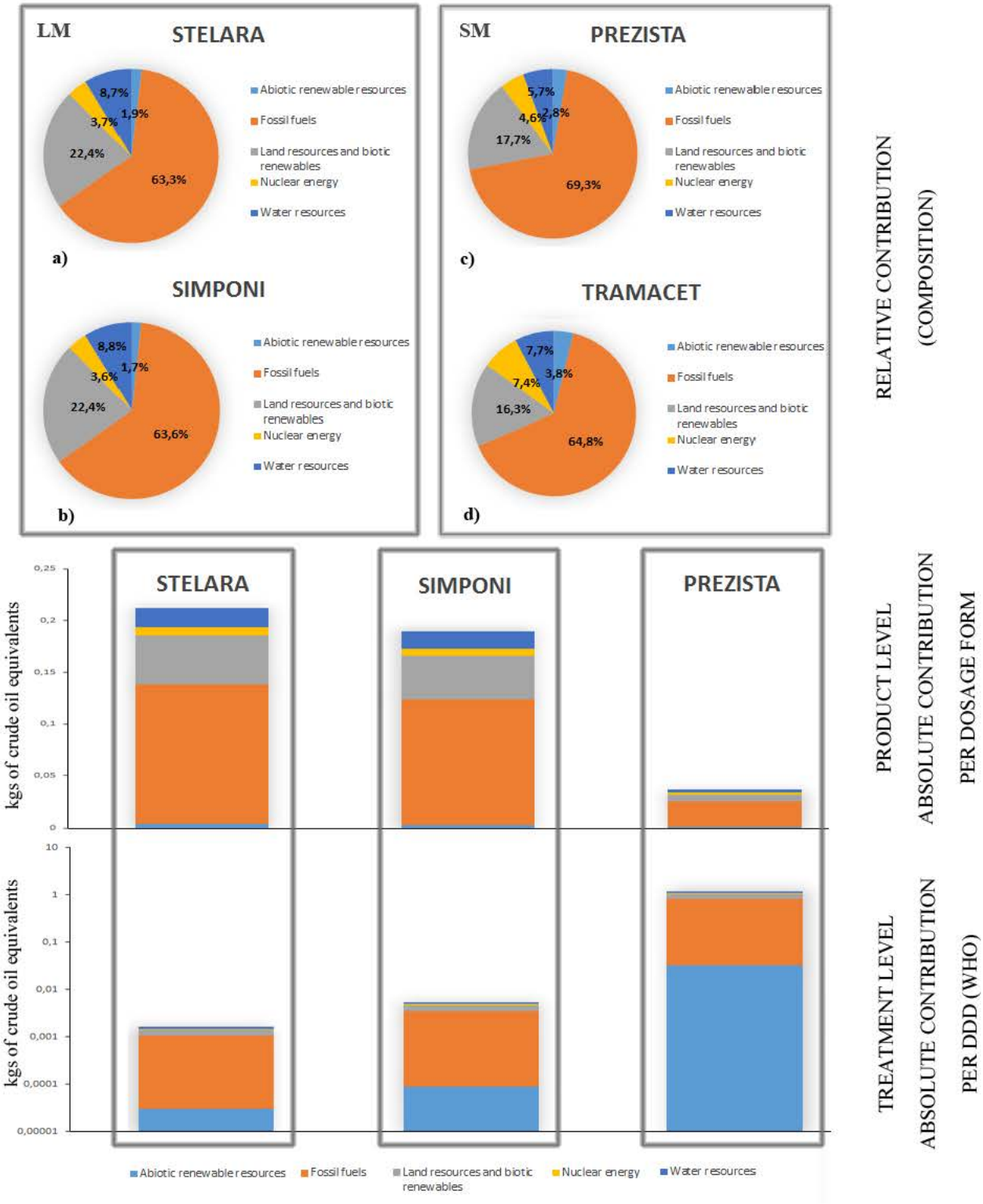
LM
STELARA
8,7%
1,9%
3,7%
22,4%
63,3%
Abiotic renewable resources
Fossil fuels
Land resources and biotic renewables
Nuclear energy
Water resources
a)
SIMPONI
8,8%
1,7%
3,6%
22,4%
63,6%
b)
SM
PREZISTA
5,7%
2,8%
4,6%
17,7%
69,3%
c)
TRAMACET
7,7%
3,8%
7,4%
16,3%
64,8%
d)
RELATIVE CONTRIBUTION
(COMPOSITION)
STELARA
SIMPONI
PREZISTA
kgs of crude oil equivalents
0,25
0,2
0,15
0,1
0,05
0
10
1
0,1
0,01
0,001
0,0001
0,00001
PRODUCT LEVEL
ABSOLUTE CONTRIBUTION
PER DOSAGE FORM
TREATMENT LEVEL
ABSOLUTE CONTRIBUTION
PER DDD (WHO)
Abiotic renewable resources
Fossil fuels
Land resources and biotic renewables
Nuclear energy
Water resources

Figure 17: Representing on top the relative contributions (composition) of the resource footprint of Large Molecules (LMs) STELARA® (a) and SIMPONI ® (b) (left) and Small Molecules (SMs) PREZISTA® (c) and TRAMACET® (d) (right). The bar charts are illustrating the absolute contributions per Dosage Form (DF) at product level and per Defined Daily Dose (DDD) at treatment level for the upper and lower bar charts respectively. For the sake of comparability, only the medicines treating immune deficiency diseases are used for absolute comparisons. The y axis of the bar charts is expressed in kg of crude oil exergy equivalents. The y axis for the comparison at treatment level are log transformed for the sake of a clear presentation.

would consume less fossil resources. Lower volumes, less chemicals and very often aqueous solvents are used instead of the very fossil intensive solvents consumed in chemical synthesis. Besides, a cell culture is being cultivated with medium that contains sugar based components indicating more land use. However, these expectations were all but trending in the results. In contrast to what was expected, Figure 17a) and b) show very similar results to Figure 17c) and d). The relative contribution of fossil resources is only moderately lower in the production of LMs (MABs) compared to SMs (on average 63.5 compared to 67.1%). This is due to the fact that fermentation processes to cultivate the cells typically take about 45 days in case of STELARA® and 60 days in case of SIMPONI®. First, fermentation requires electricity for heating the vessel jacket. Second, following GMP compliance, LM production requires a grade A to grade C cleanroom, according to the GMP classification (which in this case corresponds to 20 to 45 air changes per hour depending on the room) (European Commission, 2008). Maintaining these conditions for 45 or 60 days consumes electricity and natural gas to operate at the required Heating, Ventilation and Air Conditioning (HVAC). To illustrate the contribution of HVAC, 57.0% of all electricity used through the supply chain of

STELARA® is consumed by HVAC, of which 50.0% in upstream operations (mainly fermentation) and 7.0% in downstream operations such as harvesting and separation. The contribution of land use and biotic renewables though, proved to be only moderately higher in case of LMs (on average 22.4 compared to 17.0%) due to what was postulated above (starch and sugar based excipients in medium solutions, bigger packaging devices on a unit base, etc.). From this analysis, it was to be concluded that the relative resource footprinting of LMs is much more fossil dependent than what was expected and that the contribution of land use and biotic resources (bio) was all but dominating.

Focusing on the autoimmune disease portfolio and looking at the absolute numbers per Dosage Form (DF) (product level), i.e. Active Pharmaceutical Ingredient (API) production, Drug Product Production (DPP), Delivery Device Production (DDP) and packaging, STELARA® has the highest resource footprint followed by SIMPONI® and PREZISTA® (0.21, 0.19 and 0.06 kg crude oil-Eq respectively). The difference between the two MABs and PREZISTA® is not surprising. While PREZISTA® is a relatively dense blister packed tablet, using wet granulation or direct compression, the amount of natural resources needed is to be allocated over the amount of tablets packed in the number of blisters in one folding box. STELARA® and SIMPONI® are parenterals with a high footprint related to Delivery Devices Production (DDP) as well, such as the safety injector (use of metal springs, HDPE, PE, glass fibers for the syringe, rubber components, etc.). Next, a rather complicated folding box is used to pack only one syringe. The reason why the production of SIMPONI® still has a lower footprint than STELARA®, notwithstanding an extra fermentation time of 15 days, is the higher yield

(grams of product after first Direct Product Capture, DPC) and a more efficient chromatography in the downstream process to separate the MABs from the rest of the harvested media.

It should be stressed that from a functionality and efficacy point of view one has to include the treatment effect for the respective disease patterns (Debaveye et al., 2016). While for instance HIV patients need to swallow an 800mg PREZISTA® tablet every day, STELARA® only requires 6 injections a year to treat severe psoriasis plaque. This is reflecting the technological functionalities of long acting parenterals (e.g. proteins such as MABs) and has to be taken into account in the assessment. To include this aspect, we use the DDD as defined by the WHO and explained in the methodology section (WHO Collaborating Centre for Drug Statistics Methodology, 2015). The lower part of Figure 17 represents this and the result is remarkable (mind that the y-axis is log transformed in this graph). On a DDD basis (treatment level), the absolute consumption of natural resources is 0.0016, 0.0054 and 1.2 kg crude oil-Eq for STELARA®, SIMPONI® and PREZISTA® respectively (treatment level). On a yearly basis, the resource footprint of treating HIV with PREZISTA® is 750 times lower than treating psoriasis plaque with STELARA® because of the long acting platform enabled by MAB injectables. It should again be stated for the sake of completeness that this is an indication of how technology platforms are performing rather than a comparison of single medicines. From a Life Cycle Thinking (LCT point of view), one should be careful in generalising results and extrapolating to drugs with other functionalities.

5.4 Conclusions and Outlook

First, related to natural resource footprinting, this study revealed that the relative footprint of biologicals is not so much shifting towards the 'bio' feedstocks as expected. Producing LMs – and in particular MABs – is still a very fossil resource intensive series of operations. Second, it was proven that it is of utmost importance to take into account the functionality of the (pharmaceutical) product under analysis to make a fair comparison. One could say that, due to the character of the long acting platforms, the LMs under analysis are not only emerging from the medical 'undruggable' space perspective, but are having a lower footprint on a yearly treatment basis compared to conventional SM chemical synthesis as well and can thus be considered as more environmentally sustainable. More cases should be assessed to yield more generic results and clearly system boundaries should be expanded to optimise the Functional Unit (FU) for comparability.

Related to future research, the author shares some key messages or main learnings/bottlenecks below. First of all, because of the very data intensive analyses, a lot of process and procurement data that would affect the results of an LCA is still hardly available on many LM production sites: the use of single use equipment and discharge patterns, allocation of buffer media consumption to the specific downstream chromatography steps for purification, etc. In terms of what is better from an environmental perspective, single use bags and equipment versus reusable reactors and columns is still an unsolved question. All but least is the challenge to tackle the very high contribution of HVAC as it is the highest contributor to fossil resources and the complete footprint in general. It should be investigated if a recycling rate that high is really necessary from a compliance point of view to remove all particular matter and

potential pathogens in this very contained manufacturing environment. Another development of major importance is the breakthrough of innovation in process intensification through continuous manufacturing (e.g. continuous lyophilisation) that could potentially lower the footprint due to smaller room volumes, contained equipment, lead times, etc. In SM production, continuous manufacturing is to be considered as the major breakthrough of this decennium. This research has pioneered in the environmental resource footprinting of LM production and has postulated recommendations for further technological developments that could foster sustainable development of the biologics business in the pharmaceutical industry.

Part 3: Enhancing the Business Value of Environmental Sustainability Assessments

Chapter 6 Needs and Bottlenecks in Sustainability Assessments in Global Pharmaceutical Supply Chains

Partly redrafted from:

De Soete, W., Jiménez-González, C., et al. (2016). "Challenges and Recommendations for Environmental Sustainability Assessments of Pharmaceutical Products in the Healthcare Sector." Green Chemistry **submitted**.

6.1 Introduction

The aim of this chapter, conducted during an intensive study period at 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 sustainability assessments, to share experiences and connect professionals and eventually to identify needs, bottlenecks and priority action points for businesses and policy. This is accomplished through; (1) a stakeholder survey; (2) expert interviews and (3) roundtable discussions with sustainability professionals in the field (Figure 18). In order to create a high leverage effect and a broad encouragement of the outcomes, a variety of stakeholder communities were consulted: (1) private organisations; (2) policy and governmental research and decision support bodies; (3) NGOs; (4) universities and research institutions; (5) sector federations, agencies and consortia and last (6) consumers (hospitals, pharmacists, patients, physicians and GPs).

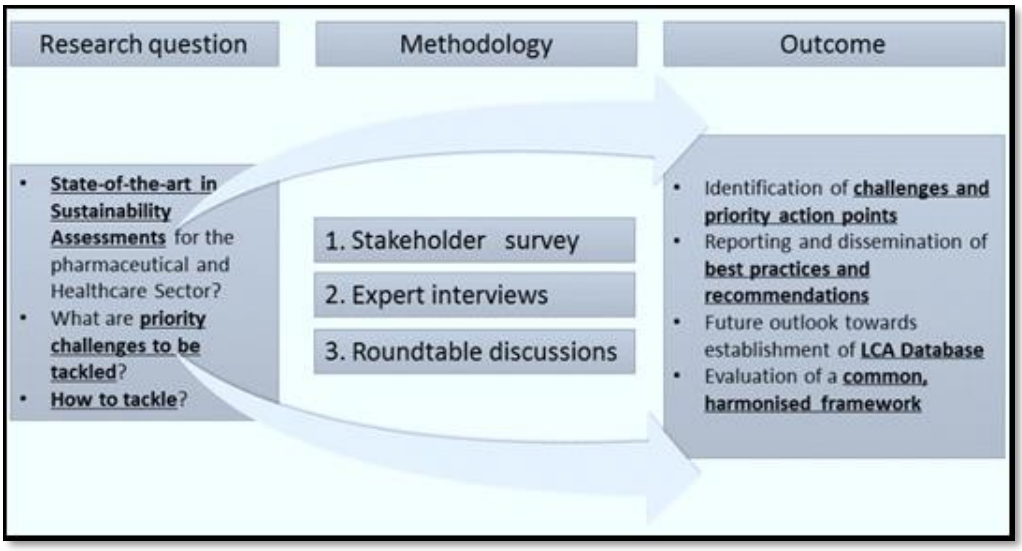

Figure 18: Schematic representation of the study outline: (1) research questions; (2) methodologies and (3) envisaged outcomes.

6.2 Methodology

6.2.1 Expert interviews

For this study 13 field experts were approached 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 statement 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.

6.2.2 Stakeholder survey

Concerning the stakeholder survey, the author 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, physicians). 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 responses 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). A unique identifier is defined as an individual or group of individuals representing a legal entity that equals a unique entry in the database of potential participants (i.e. the 340 potential participants covered 174 unique legal entities). Table 7 in Chapter 6.3.2 provides more details about invitations, unique identifiers and responses. Figure 19 gives an overview on the aggregation ratio per stakeholder group. The stakeholder survey itself that was circulated is to be found in Annex A5.

6.2.3 Roundtable discussions

The roundtable discussions were organised in Q4 of 2015 at the JRC's Institute of Environmental Sustainability, Sustainability Assessment Unit (IES SA). 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.

6.3 Results and Discussion

6.3.1 Expert interviews

Many of the challenges and focus points that were drawn from the literature study were taken up as key issues/questions in these expert interviews. The next paragraphs will highlight the visions and best practices obtained from the expert interviews according to four predefined discussion topics.

6.3.1.1 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 (Debaveye et al., 2016). Expanding the system boundaries from product level (manufacturing) to product-service level (healthcare pathway) 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 development decision trees and stage-gating processes (De Soete, 2016). While streamlined LCA (e.g. FLASC tool, and De Soete et al, 2014) is more and more being applied in early research phases together with qualitative measures (e.g. preferred solvents, toxic substances evaluation, etc.), full-blown resource based LCA is used for optimizing case studies in retrofitting or for the evaluation of second and third generation medicines.

In terms of sourcing and quality assurance of outsourced LCAs to third parties, a lot of private entities see value in cooperating 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 threat on central data management of LCIs.

6.3.1.2 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 bullet wise below. These were gathered from interviews with the experts involved in this research.

- Stakeholder involvement: In the light of improving data quality and enhancing the use of primary Life Cycle Data (LCD), both upstream and downstream 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 device and packaging suppliers. Downstream actors are e.g. logistic suppliers, hospital networks, wholesalers, national health services and in the end the patient. 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. The system boundaries need to be aligned to 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 Levels (TRLs). 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. the Disability-Adjusted Life Years or DALY concept) but are less reliable in terms of model and data 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 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 (PIE): Unfortunately, very little is known about what happens with pharmaceutical residues and metabolites after the use phase of the product. For some pharmaceuticals, characterisation factors were established through exposure, fate, effect and damage factors (Alfonsín et al., 2014). The PHARMAS FP7 project is one of the few 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 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.

6.3.1.3 Tackling life cycle inventory data unavailability from suppliers and vendors through the value chain

The general consensus on data sharing 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 the 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, FLASC™) and databases

(Curzons et al., 2007; Weidema, 2012; Ciroth et al., 2013). 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). Referring to other sectors, Plastics Europe took the very same role as the first European Sector Federation representing a 'Node' for the plastics industry. 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.

6.3.1.4 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 oil 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 and Medical Devices, 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 is merely depending on the market to be served (Bilan Carbone for France, NHS Guidance/BSI for the UK, etc.) which shows

the emergence of a standardised method 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 range of impacts 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 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 author would like to make the remark here that these ranges will tend to decrease when more LCI data is available. The LCI and impact assessment issue is inherently connected to each other and is to be seen as a major future challenge.

6.3.2 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 scientific literature, the authors have sent out stakeholder surveys (to be found in Annex A5) 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, GPs). 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 responses 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 (explained in Chapter 6.2.2), yielding a response rate of 24% (41 responses). Table 7 provides a more detailed analysis of the involved stakeholder groups, the amount of invitees, the amount of aggregated invitees per legal entity, the absolute amount and percentual aggregated responses per legal entity and finally the response rate per invited legal entity.

Table 7: Stakeholder invitation statistics and response rates: (1) Individual invitees (#): absolute amount of invited individuals per stakeholder group; (2) Aggregated invitees (#); (3) Aggregated responses (#); (4) Aggregated responses (%); (5) Response rate per invited entity (%)

Stakeholder Group	Individual invitees (#)	Aggregated invitees (#)	Aggregated responses (#)	Aggregated 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 weighted percentage	340	174	41	24	-

The ratio of $\frac{Individual\ Invitees\ [\#]}{Aggregated\ invitees\ [\#]}$ is defined as the aggregation ratio per stakeholder group and is visualised in Figure 19. The rather low aggregated response rate (Figure 20b) 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) (Figure 19). 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 author reached out to the European Sector Federation EFPIA and the sector federations of the member states, which 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 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 (Figure 20a). It should be mentioned that Asia and Latin America was not included in this study, where mainly (contract) manufacturing is taking place. 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 (OECD/EU, 2014; EFPIA, 2015). 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' from the innovative medicine producers. On the other hand, once generics are one the market, it's 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 on the market.

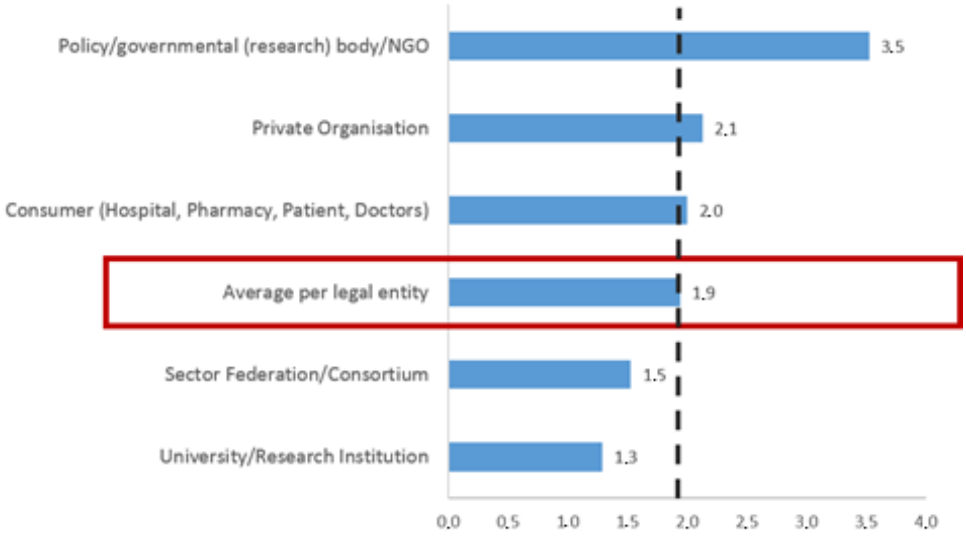

Figure 19: The x-axis represents the aggregation ratio per stakeholder group (with an average of 1.9 indicated by the vertically dashed line) defined as the amount of invitees divided by the amount of aggregated invitees. The y-axis represents the different stakeholder groups (with the average per legal entity indicated by the red box).

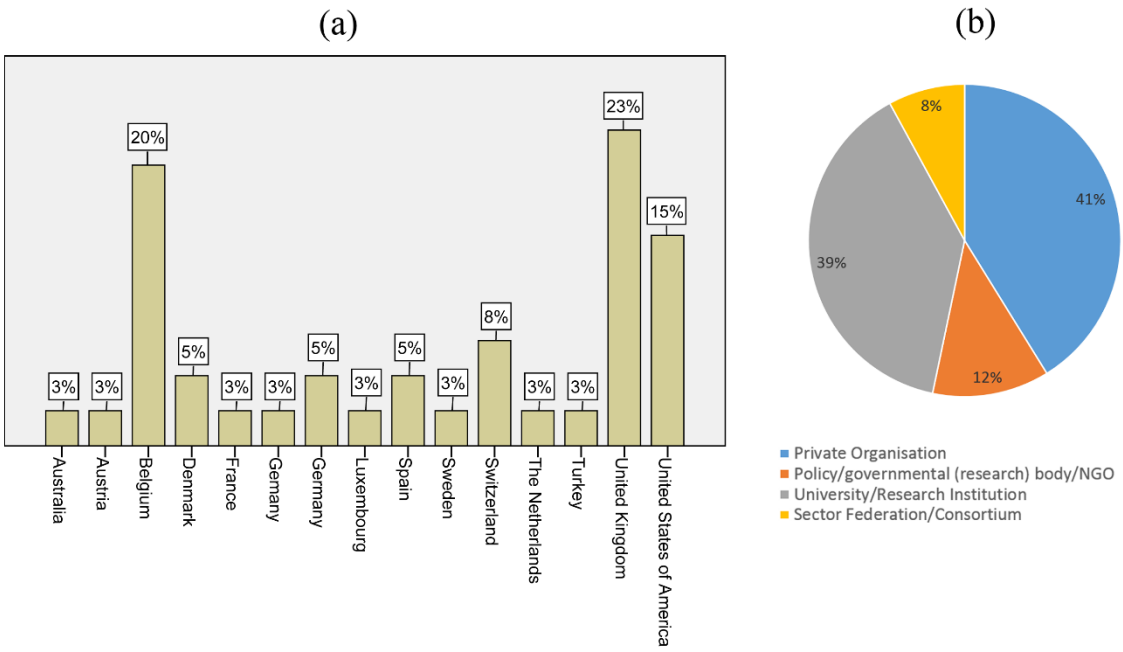

Figure 20: (a) Geographical spread of the responses. The United Kingdom, Belgium and the United States of America pop out. It should be mentioned that Asia and Latin America was not included in this study, where mainly (contract) manufacturing is taking place. The authors were able to link a high R&D activity with a high sustainability and compliance awareness; (b) Aggregated percentual response rate per stakeholder group.

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). The next paragraphs elaborate on the output generated by the stakeholder survey, subdivided in the three aforementioned thematic fields.

6.3.2.1 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). 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 B2C communications (24%). Remarkable is that 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 material, the pharmaceutical and healthcare industry is a rather closed community. However, this is gradually changing and there is a definite need to tackle data life cycle data unavailability, to improve data transparency and reliability, etc. As was already touched upon in the results section from the expert interviews, the participants generally do not think that a Product Category approach is the way forward. 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 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 (PIE). Some studies were performed deriving

characterisation factors for EoL scenarios of API excretion, however this has not been done for metabolites so far (Alfonsín et al., 2014; Li et al., 2016). Probably the most lively topic related to the goal and scope of an LCA is the applied Functional Unit (FU) (Ciroth and Srocka, 2008). 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 (Grießhammer et al., 2005). 76% of all participants acknowledge 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, …) 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.

6.3.2.2 Life Cycle Data Inventory

As has been touched upon in Chapter 6.3.1.3 dealing with data life cycle data 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 remains 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 participants were questioned 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 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). The Network allows for flexibility while facilitating the availability of LCD from different organisations and sources (Sanfélix et al., 2013; Recchioni et al., 2015). 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 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.

6.3.2.3 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 chapter, 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 correlate with climate change indicators such as the IPCC CF (Huijbregts et al., 2006; Huijbregts et al., 2010; De Soete et al., 2014b). Water consumption and human toxicity proved to be relevant impact categories in expressing the environmental impact of pharmaceutical production processes (additionally in relation with the human health benefits) (Debaveye et al., 2016). 56% of the healthcare LCA practitioners never use endpoint indicators related to the three Areas of Protection (AoP). Human health, natural resources and ecosystems 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.

6.3.3 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 & 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 matchmaking 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 hold on key topics that arouse 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 author 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 (Penny et al., 2015). Assessing full healthcare pathways allows for identifying burdens within holistic system boundaries (e.g. HVAC at

hospitals) 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.

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 held operational at the level of the (European) sector federations such as 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 highly 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 (De Soete, 2016; Kralisch et al., 2016). The author strongly stimulates further development in merging 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, the International Reference Life Cycle Data System (ILCD) Handbook, the guidelines from the World Business Council on

Sustainable Development (WBCSD), etc. (European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010; European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2012; NHS Sustainable Development Unit, 2012; World Business Council on Sustainable Development, 2016). There is a clear need to harmonise further developments instead of making solutions even more diffuse for different stakeholders. The European Commission's Product Environmental Footprint (PEF) Guidelines might be a good alternative, following on the ILCD Handbook (European Commission, 2013). However, at this stage, the PEF and Organisation Environmental Footprint (OEF) at corporate level are still in pilot testing phase. The pharmaceutical sector is not subject of any of those pilots, but should be able to grasp learnings (pro's and con's) 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.

6.4 Conclusion and Outlook

This chapter is the result of the work of many participant groups and devoted individuals to bring sustainability assessments of pharmaceuticals products or services within the healthcare sector to the next level. Through expert interviews, stakeholder surveys and roundtable discussions, the team 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 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, new developments were highlighted 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 team strongly suggest and will keep on facilitating roundtable discussions and debates (e.g. at EFPIA, NHS SDU, etc.). Next, the team urges 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 all stakeholders involved that this study should be used as a guidance to steer further research and development in industry, academia and policy in order to serve and support decision making processes.

Chapter 7
Integrating Life Cycle Thinking in Early R&D Development Stages

Redrafted from:

De Soete, W., Boone, L., et al. (2014). "Environmental resource footprinting of drug manufacturing: Effects of scale-up and tablet dosage." Resources Conservation and Recycling **91**: 82-88.

7.1 Introduction

In the chemical and pharmaceutical industry, both companies and research institutes have been developing metrics and tools to assess and manage the 'greenness' of their products and services throughout the last decades. A distinction is made between process oriented indicators (e.g. E-factor, Process Mass Intensity, etc.) and life cycle oriented eco-indicators (e.g. Carbon Footprint) (Lapkin and Constable, 2009; Jiménez-González et al., 2013). With reference to green chemistry and green engineering, process indicators are traditionally used to assess and eventually enhance the environmental sustainability of products and processes; however, a life cycle approach is favoured to avoid outsourcing of burdens (Dewulf et al., 2007a). The latter includes the cumulative environmental burden exerted through all steps of the supply chain - and more generally the life cycle - of a certain product or service, including both upstream and downstream processing, ranging from raw material extraction to the End-of-Life waste treatment (Azapagic, 1999; Russell et al., 2005). A more elaborated view on metrics, assessment methods, etc. was given in Chapter 1. Next to the development and profound elaboration of assessment methods with respect to the pharmaceutical industry, some fast assessment tools were developed to estimate the environmental sustainability of Active Pharmaceutical Ingredient (API) production processes (Curzons et al., 2007; Wernet et al., 2009). These generic tools, typically circumventing the need for an in-depth process analysis, rely on empirical models built on rather scarce confidential data. A more detailed, less generic model was developed at Ghent University in order to evaluate the integrated resource consumption of a multipurpose pharmaceutical production plant of the Janssen Group, Johnson & Johnson (Van der Vorst et al., 2009a; Van der Vorst et al., 2011). Taking into account the Drug Product (DP) production process (pharmaceutical production step in which the API is formulated in combination with

various excipients in a so-called dosage form), the American Chemical Society (ACS) Green Chemistry Initiative Pharmaceutical Roundtable (GCIPR) developed a simplified, mass accounting fast Life Cycle Assessment (LCA) tool (Jiménez-González et al., 2013).

With aforementioned assessment tools, an important step was taken towards generic environmental sustainability assessments of pharmaceuticals. However, these tools do not yet account for the early and late development stages of a pharmaceutical drug product, which typically comprise abound 14 out of 20 years of the patent term (Rees, 2011; Ellery and Hansen, 2012). Moreover, they cannot predict future environmental impacts at industrial scale when the pharmaceutical is at an early development stage. This forecasting perspective should be embedded in a tool aiming at the provision of eco-indicators intended for integration in R&D decision trees (De Soete et al., 2013). This way, one can anticipate on the environmental burden of even first generation medicines by including eco-indicators as criterion for decision-making at important development stages or stage gates, next to drug bio-availability, patient compliance, cost-effectiveness, etc. The predictive impact assessment can be accomplished through evaluation of environmental burdens of production technologies at different production scales (e.g. lab scale, clinical production scale, pilot scale, industrial manufacturing scale). Note that in other sectors (e.g. the energy sector) power-law relationships were already established in order to predict e.g. the fuel consumption and costs of energy conversion technologies (Caduff et al., 2010; Caduff et al., 2012).

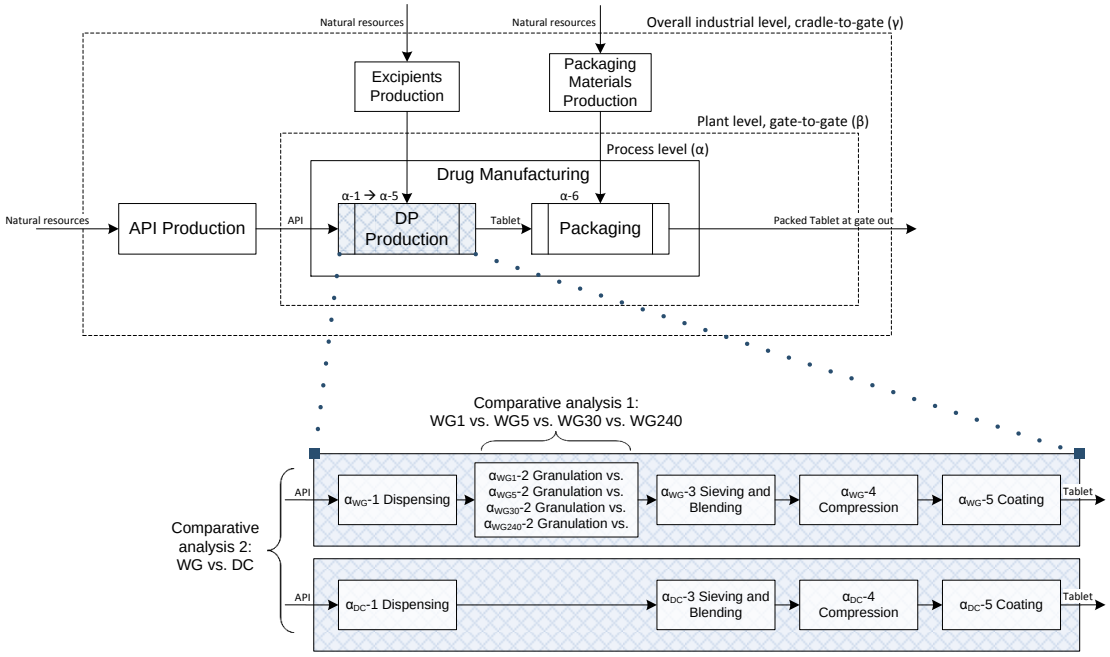

Figure 21: Pharmaceutical drug manufacturing supply chain, represented within the triple system boundary approach: process level (α), plant level (β) and overall industrial level (γ). Comparative analysis 1 and Comparative analysis 2 represent the two main objectives of this chapter: Comparative environmental sustainability assessment of four consecutive scales of tablet manufacturing through Wet Granulation (WG1 versus WG5 versus WG30 versus WG240) (Comparative analysis 1) and comparative environmental sustainability assessment of PREZISTA® 800 mg (WG) versus PREZISTA® 2 x 400 mg (Direct Compression, DC). Note that utility production (e.g. electricity, heating media, etc.) is not represented in this figure for the sake of simplification.

The objective of this chapter is twofold. First of all, it analyses cumulative resource consumption of pharmaceutical tablet manufacturing of PREZISTA® 800 mg through Wet Granulation (WG) at four consecutive scales (WG1 = 1 kg/h, WG5 = 5 kg/h, WG30 = 30 kg/h and WG240 = 240 kg/h resp.) and proposes the experience curve (Figure 21). PREZISTA® is a well-known second-generation protease inhibitor used to slow down Human Immunodeficiency Virus (HIV) infections. This typically high weight tablet requires wet granulation by capillary and viscous forces to enhance the flowability of the powder mix and finally its tablet properties as is explained in Chapter 4.1 (Franch-

Lage et al., 2011). Second, the study conducted for this chapter evaluates the environmental impact from a life cycle perspective of a daily consumption of PREZISTA® 2 x 400 mg versus the bioequivalent 800 mg which was launched to enhance patient compliance. This tablet allows patients to take only one tablet once a day instead of taking two 400 mg tablets per day. In contrast to the PREZISTA® 800 mg tablet, production of the PREZISTA® 400 mg tablet covers Direct Compression (DC) of the powder mix, yielding good tablet properties as presented in Figure 21. Environmental sustainability assessment in this study was conducted at three different system boundaries, which enables identification, localisation and eventually reduction of environmental burdens, in this case resource extraction. Exergy Analysis (EA) was used at process level (α) and plant level (β) while a cradle-to-gate Exergetic Life Cycle Assessment (ELCA) was conducted at the overall industrial level (γ) (Dewulf et al., 2007a; Dewulf et al., 2008). Life cycle stages taken into account are API production, DP production and Packaging (Figure 21).

7.2 Methodology

In pursuit of harmonisation in reporting methodology of a Life Cycle Assessment (LCA), the following paragraphs briefly elaborate the chosen methodological framework according to the ILCD Handbook Guidelines (European Commission - Joint Research Centre - Institute for Environment and Sustainability, 2010).

7.2.1 Functional Unit (FU)

In order to provide a reference to which all inputs and outputs are normalized, the Functional Unit (FU) or final demand of the product system was defined as one daily intake of PREZISTA®. Given that the PREZISTA® 800 mg tablet is bioequivalent to two PREZISTA® 400 mg tablets (both representing one daily intake of the patient), this functional unit is valid for both research questions from a life cycle thinking point of view.

7.2.2 Product System and its System Boundaries

The considered product system is visualised in Figure 21. It comprises Active Pharmaceutical Ingredient (API) production, Drug Product (DP) production and Packaging of PREZISTA® at the overall industrial level (γ, cradle-to-gate). At process (α) and plant (β, gate-to-gate) level the focus lies on DP production and Packaging since none of the proposed research questions affect the API synthesis steps in any way. At the point at which DP development and DP scaling to larger batches is initiated in a development project, the scale-up of API synthesis has reached a rather mature state (Gad, 2008; Janssen Pharmaceutica NV, 2013). Consequently, through this study, the production scale of API was assumed to be constant at full manufacturing scale. In the first comparative analysis DP production comprises five core processes: Dispensing (α_{WG-1}); Wet Granulation (WG) (α_{WG-2}); Sieving and Blending (α_{WG-3}); Compression (α_{WG-4}) and eventually Coating (α_{WG-5}), of which each is subdivided into different separated subprocesses. The comparative character of this first research question (effect of scale-up and learning on cumulative resource consumption) is to be found in the complete Drug Product (DP) production system of which four scales of production are investigated. This means that Dispensing (α_{WG-1}), Wet Granulation (WG) (α_{WG-2}),

Sieving and Blending (α_{WG-3}), Compression (α_{WG-4}) and eventually Coating (α_{WG-5}) is influenced by the scale-up of the process. The three smallest production scales WG1, WG5 and WG30 are located at the R&D facilities of the Janssen Group (Johnson & Johnson) in Beerse, Belgium. The industrial manufacturing scale WG240 is operated at the manufacturing site of the Janssen Group in Gurabo, Puerto Rico. In the Direct Compression (DC) scenario of the second comparative analysis, the wet granulation step disappears. Using SPSS Statistics, a power-law experience curve was established for this manufacturing technology at plant level (β). An experience curve accounts for the scaling effects and learning effects (efficiency gains in technology over time) since easily 10 years can lay between testing at lab scale and full scale implementation in a manufacturing environment. All aforementioned core processes need to be supplied with process utilities which are produced at the production plant within the gate-to-gate level (β) (e.g. steam production in on-site natural gas boilers) or outsourced to the overall industrial level (γ) (e.g. Belgian grid electricity production mix). Utility production and interrelated background processes in the industrial metabolism (indirect resource demand) are not visualised in Figure 21.

7.2.3 Life Cycle Inventory (LCI)

Foreground data at process (α) and plant (β) level were gathered at the Janssen site in Beerse, Belgium, except for the industrial manufacturing scale (WG240). Data of the latter wet granulation system were gathered at the Janssen-Cilag SpA manufacturing plant in Latina, Italy, which were used as a proxy for the matching wet granulation system in Gurabo, Puerto Rico, except for the outsourced production (e.g. electricity production). During the timeframe of the project, it was not possible to analyse the production plant in Puerto Rico. However, the foreground production process is exactly

the same in Latina (Italy) as in Gurabo (Puerto Rico). Both production sites of Johnson & Johnson are equipped with a large scale top spray fluid bed granulator, consuming a fairly equal amount of resources, except for spatially differentiated background processes (e.g. electricity production). Targeted data to derive environmental stressors were found in operational batch reports, validation reports, cleaning procedures, equipment manuals, P&IDs, commissioning files, MSDS files, Bill of Materials (BOM) and economic procurement data (see Table 3 in Chapter 4.2.4). With these data, mass and energy balances could be established to be used in the qualification and quantification of interactions of the process and plant level with the industrial metabolism. Background data for the processes in the industrial metabolism at γ level were extracted from the ecoinvent v2.2 database (Frischknecht and Rebitzer, 2005), except for the API synthesis. Data on the API production processes were retrieved out of a range of formerly conducted studies of similar synthesis steps (some of them carried out at the same plant) as an average proxy since no ecoinvent data was available (Van der Vorst et al., 2009a; Wernet et al., 2010; De Soete et al., 2013; Van der Vorst et al., 2013). This way, resource extraction was calculated back to the extraction of elementary natural resources to be characterized in the Life Cycle Impact Assessment (LCIA).

7.2.4 Impact Categories

The analysis conducted at process (α) and plant (β) level was performed through Exergy Analysis (EA) evaluating the quantity and quality of material and energetic resource consumption based on the second law of thermodynamics (Apaiah et al., 2006; Hammond, 2007). At cradle-to-gate (γ) level, the environmental stressors affecting the resource use impact category were quantified by the Cumulative Exergy Extracted from the Natural Environment (CEENE), subdividing resources in seven subcategories. This

Life Cycle Impact Assessment (LCIA) method covers (1) Renewable resources other than biomass, (2) Fossil resources, (3) Nuclear energy, (4) Metal ores, (5) Minerals and mineral aggregates, (6) Water resources and (7) Land occupation and biomass production (De Meester et al., 2006, Dewulf, Bösch, 2007a). More detailed information about EA and ELCA was presented in Chapter 1.4 and 4.2.6.

7.2.5 Calculations

The calculation methods used to compute the exergy content of resources was already described in Chapter 4.2.6. What follows below is a very brief overview of the most important principles and formulas. At process (α) and plant (β) level, the chemical exergy content of components was computed based on the reference conditions introduced by Morris and Szargut (1986). For organic chemicals, the group contribution method was used. As for inorganics, the Gibbs free energy of formation was calculated and taken into account (Szargut et al., 1988; Szargut et al., 2005). The physical exergy of material and energetic resources (e.g. hot water and steam) was calculated according to the following formula:

$$Ex^{PH} = (H - H_0) - T_0 \times (S - S_0) \quad (27)$$

in which H_0, T_0, S_0 are the enthalpy, the temperature and the entropy at its reference state (T_0 = 298.15 K and p_0 = 101.325 kPa) respectively (Szargut et al., 2005). H and S are the respective enthalpy and entropy of the stream under consideration. The following derivation was used to calculate the physical exergy content of compressed air:

$$ex^{PH} = \left| c_p \times \left[(T - T_0) - T_0 \times \ln \frac{T}{T_0} \right] \right| + \left| R \times T_0 \times \ln \frac{p}{p_0} \right| \quad (28)$$

in which c_p is the isobaric specific heat capacity of air, R the universal gas constant and T_0 and p_0 the temperature and pressure of the reference state respectively (Cornelissen

and Hirs, 2002). T and p are the respective temperature and pressure of the compressed air volume.

7.2.6 Assumptions and Limitations

Conducting a combined process and life cycle analysis implies the inclusion of a large quantity of interrelated processes and production factors or environmental stressors (e.g. resource use, land use, etc.) in the industrial metabolism (in this case specifically the fine chemical, pharmaceutical and energy sectors). In accounting for the indirect demand of the industrial background system to produce one functional unit (daily intake), one inherently adopts process specific assumptions and limitations with respect to the ecoinvent background database or formerly conducted studies regarding geographical location, time horizon, production scale, etc. In conducting this LCA, specific attention was paid to outsourced utility production such as electricity production, especially in the case of WG240, where the pharmaceutical manufacturing site of Gurabo (Puerto Rico) was taken as a proxy for the Latina site (Italy). Zooming in on the foreground system, fewer assumptions needed to be made since more specific process data were available. For all scenarios process and site specific data were inventoried and used in the analyses, except for the manufacturing at full scale (WG240). For the latter system process specific data were retrieved from Chapter 4.2.4, in which the same top spray fluid bed granulation process was analysed at a pharmaceutical manufacturing site of the Janssen Group in Latina, Italy (De Soete et al., 2013). The rationale for this approximation was mentioned above in the description of the product systems.

7.3 Results and Discussion

7.3.1 Scale-up and learning effects of pharmaceutical tablet manufacturing

Quantitative thermodynamic analysis of all core processes in Drug Product (DP) production and Packaging (e.g. dispensing, wet granulation, mixing and blending, compression, coating, etc.) required in the manufacturing of PREZISTA® 800 mg by Wet Granulation (WG) at four consecutive scales (resp. WG1 = 1 kg/h, WG5 = 5 kg/h, WG30 = 30 kg/h and WG240 = 240 kg/h) yielded mass and energy balances and eventually exergy balances at the three system boundaries. The latter results in a quantified total exergetic resource consumption (MJ_{ex}/daily intake), which is shown in Figure 22. The authors opted for a functional classification of resources according to the following subdivision: (1) Active Pharmaceutical Ingredient (API); (2) Excipients; (3) Packaging materials; (4) Electromechanical resources; (5) Compressed air; (6) Heating media and (7) Cleaning media.

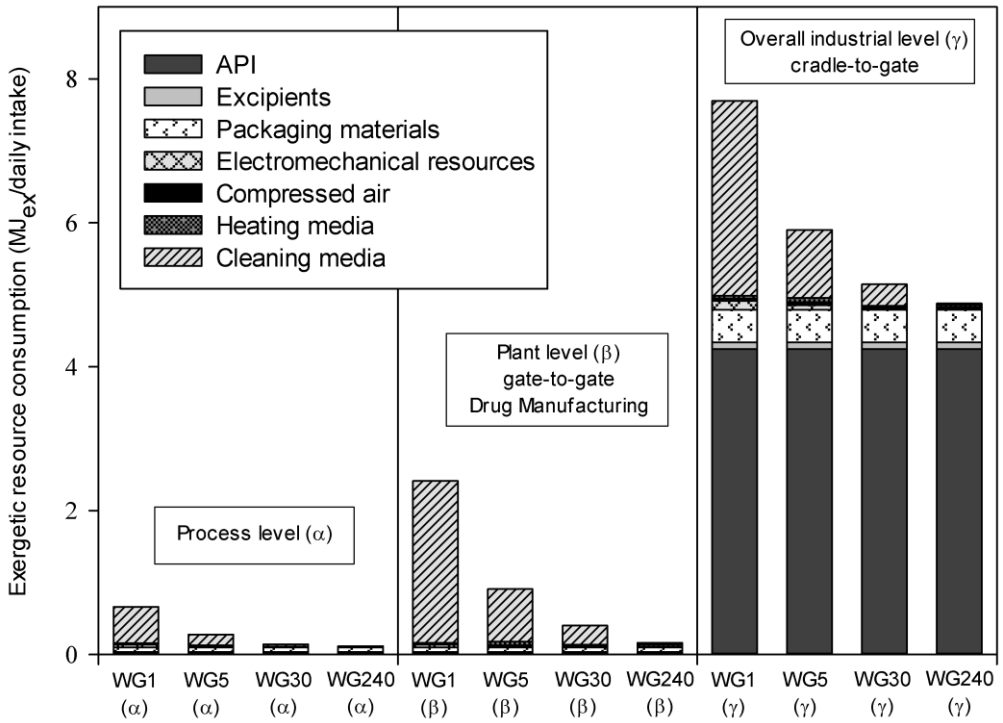

Figure 22: Cumulative exergetic resource consumption (MJ_{ex}/daily intake) of four consecutive production scales of PREZISTA® 800 mg tablet manufacturing by means of Wet Granulation (WG) (resp. WG1 = 1 kg/h, WG5 = 5 kg/h, WG30 = 30 kg/h and WG240 = 240 kg/h). Results are shown in functional categories at process level (α), plant level (β) and overall industrial level (γ) respectively. The consumption and production of cleaning media (hot water, Cleaning in Place, detergents, etc.) proved to possess the highest influence on the experience curve scope.

At process level (α), total resource extraction for the manufacturing of one daily dose of PREZISTA® (in this case one 800 mg tablet) amounted up to 0.44 MJ_{ex} at smallest scale (WG1) while this amount proved to be reduced by 58, 79 and 83% at WG5, WG30 and WG240 respectively (Figure 22, Table 8). Since more or less the same amount of feedstock materials is needed in the production of one single tablet at different scales (apart from minor mass yield changes in the tablet production and material losses due to handling and storage), the reduction in integral resource consumption in the scale-up of technologies is due to a more efficient production, supply and use of process utilities. In this case, the reduction in resource use is due to a reduced consumption of

electromechanical resources and compressed air, next to more efficient heating processes (e.g. electrical heating versus natural gas) and more advanced cleaning procedures (e.g. Cleaning in Place, CIP at larger production scales).

Table 8: Percentage reduction of integral resource consumption at scales WG5, WG30 and WG240 (%) (Reference: WG1).

	α (process level)	**β (plant level)**	**γ (overall industrial level)**
WG5	58	62	23
WG30	79	83	33
WG240	83	93	37

Since most of the consumed utilities at process level (α) were produced at plant level (β) (e.g. steam production and hot water production as cleaning media), total resource consumption increased significantly at plant level (β) when compared to process level (α). At plant level (β) the total resource extraction for the manufacturing of the 800 mg PREZISTA® tablet amounted up to 2.41 MJ_{ex} at smallest lab scale (WG1), 0.91 MJ_{ex} at WG5, 0.40 MJ_{ex} at WG30 and 0.16 MJ_{ex} at industrial manufacturing scale (WG240). Percentage reductions of integral resource consumption with reference to the smallest lab scale setup (WG1) are listed in Table 8. Figure 22 shows the remarkably high contribution of cleaning media to the total exergetic resource demand at small scales within these system boundaries (gate-to-gate). Taking into account the applied functional unit (one daily intake), more cleaning cycles were needed to produce a certain amount of daily intakes compared to production at larger scale. Furthermore, for heating of cleaning media, e.g. in the production of a hot water cleaning recipe, electrical heat exchangers are used at small scales, while steam heat exchangers (fed by natural gas boilers) are used in industrial manufacturing. The exergetic efficiency of the latter generally is higher compared to the exergetic efficiency of electrical heat exchangers,

which explains the contribution reduction of cleaning media to total resource extraction at larger scales (Hammond, 2007).

The aforementioned clarification explains the relatively high absolute value of the experience factor that was obtained for this technology (-0.57). In the experience curve $y = A * x^B$, x indicates the production scale in kg/h, y is the exergetic resource consumption at plant level (β) in MJ_{ex}/daily intake, while A and B stand for the exergetic resource consumption at smallest lab scale (WG1) and the experience factor respectively. A power-law experience curve $y = 2.40 * x^{-0.57}$ was obtained with a regression coefficient (R^2) of 0.99 and a 95% Confidence Interval (CI) on the experience factor (-0.57) of [-0.714 -0.416]. The sharply decreasing curve (high scaling factor) is mainly due to the inefficient cleaning steps at smaller production scales compared to the Cleaning in Place (CIP) at full manufacturing scale as was argued in the previous paragraph.

Expanding the boundaries of the product system under study to the overall industrial level (γ) reveals mainly the resource demand of outsourced burdens contained in the production of Active Pharmaceutical Ingredients (APIs), excipients, packaging materials and grid electricity (Figure 22). At smallest lab scale (WG1) it amounts up to 7.70 MJ_{ex}/daily intake of which 55% is due to the API production chain, 35% is due to the production and supply of cleaning media (highest impact of electricity production for the heating of cleaning media) and approximately 6% is due to the production of primary and secondary packaging materials. It should be kept in mind that the API production is assumed to be operated at full manufacturing scale, as stated previously. If the batch sizes of API synthesis steps are not yet at full scale or in case the synthesis route is typically a very complex one, the impact contribution of the production steps

might be even higher (Van der Vorst et al., 2011). At industrial scale (WG240), utility consumption per daily intake was reduced significantly at process level (α); consequently, the relative contribution of material resources to the cumulative resource extraction at overall industrial level (γ) is even higher. 87% of the total 4.88 MJ_{ex}/daily intake is due to the API production chain and 9% is related to the production of packaging materials. This high outsourced burden is partly due to the fact that PREZISTA® is a high dose drug. Low dose pharmaceuticals generally show a much smaller impact due to the API production steps (see Chapter 4.3.4) (De Soete et al., 2013). Next to the former subdivision of resources in functional categories, the value of material and energetic resources can be subsumed as well by their functionality at the cradle of resource extraction: (1) Renewable resources other than biomass; (2) Fossil resources; (3) Nuclear energy; (4) Metal ores; (5) Minerals and mineral aggregates; (6) Water resources; (7) Land occupation and biomass production (Figure 23). This extended footprint revealed that about 66% of all extracted resources in the production of one daily intake of PREZISTA® are fossil resources, 14% of the footprint is due to land occupation and biomass production while 8%, 7% and 4% is due to water resources, nuclear energy and renewable resources other than biomass respectively. Linking both ways of classifying resources disclosed that both API and manufacturing utilities (heating media, electromechanical power, cleaning media) are highly correlated with the amount of fossil resources required through the supply chain, whereas primary and secondary packaging materials mainly influence the contribution of land occupation induced by biomass needs. The former can be justified by unravelling the complex industrial metabolism of the API synthesis. Especially the use of solvents, working at high temperatures and complex multistep synthesis routes explain the carbon intensity of APIs. On the other hand, the latter relationship between the use of packaging materials and the contribution of land occupation and biomass to the total resource footprint is to

be clarified by the land intensive paper and cardboard production. At smaller scales, the relative contribution of fossil resources slightly increases because of the extra fuel resources needed in the production and relatively inefficient heating of cleaning media. The general trend revealed that industrial manufacturing in larger batches is less resource intensive (up to 37%).

Since all existing scales of wet granulation used in pharmaceutical tablet manufacturing were analysed and studied, it seems reasonable to recognize the power-law relationship $y = 2.40 * x^{-0.57}$ and the rather high slope of the experience curve of resource extraction in pharmaceutical tablet manufacturing when enlarging production scales. The establishment of such experience curves can trigger a closer look at the underlying - more generic - principles of scaling/learning/experience factors applied to different technologies.

7.3.2 Effects of tablet dosage; the issue of patient compliance

The development of the PREZISTA® 800 mg tablet on different scales emerged from patient compliance reasons. About half of the patients taking PREZISTA® 400 mg took PREZISTA® 2 x 400 mg at the same time to get to their required daily intake. Unfortunately, HIV patients need to take even more medicines to treat the complications of their HIV infection (e.g. pneumonia). Reducing the daily amount of pills offers a better life quality from a patient compliance point of view. As a consequence, the development of a PREZISTA® 800 mg tablet was favourable from both a social and economic point of view. Through this section, the resource oriented environmental point of view in comparing PREZISTA® 800 mg and PREZISTA® 2 x 400 is highlighted,

representing one aspect of the environmental consequences of developing PREZISTA® 800 mg.

When comparing PREZISTA® 2 x 400 mg produced by Direct Compression (DC) and PREZISTA® 800 mg produced by Wet Granulation (WG) at process level (α), a decrease in resource demand of 13% was found, mainly due to the more efficient packaging phase in the production of PREZISTA® 800 mg tablets and the use of more complex excipients in the production of PREZISTA® 2 x 400 mg tablets. However, when analysing the different production processes it seems that the process mass yield is higher in DC compared to WG. As a result, more API and excipients is needed in order to produce one daily intake of PREZISTA® 800 mg since more material is lost. The extra resources extracted from the natural environment to produce this lost amount of API and excipients elsewhere in the industrial network together with the energy intensity of the granulation step neutralize the advantages of the more efficient packaging of PREZISTA® 800 mg within the cradle-to-gate analysis. At overall industrial level (γ), the absolute amount of resource extraction in the manufacturing of PREZISTA® 2 x 400 mg and in the manufacturing of PREZISTA® 800 mg shows no significant difference (5.14 versus 5.15 MJ_{ex}/daily intake). However, out of Figure 23, it can be deduced that a shift appears in relative contributions of resource categories. As mentioned above, less API and excipients is needed in the production of PREZISTA® 2 x 400 mg via DC but the kind of excipients needed in DC is different and of higher resource quality compared to WG. More packaging materials per Functional Unit (FU) are needed in the production of PREZISTA® 2 x 400 mg compared to the production of PREZISTA® 800 mg, which evidences the higher contribution of land occupation for biomass production. In general, it could be concluded that in meeting social and

economic demands by launching the PREZISTA® 800 mg tablet, no trade-off in environmental burden occurred.

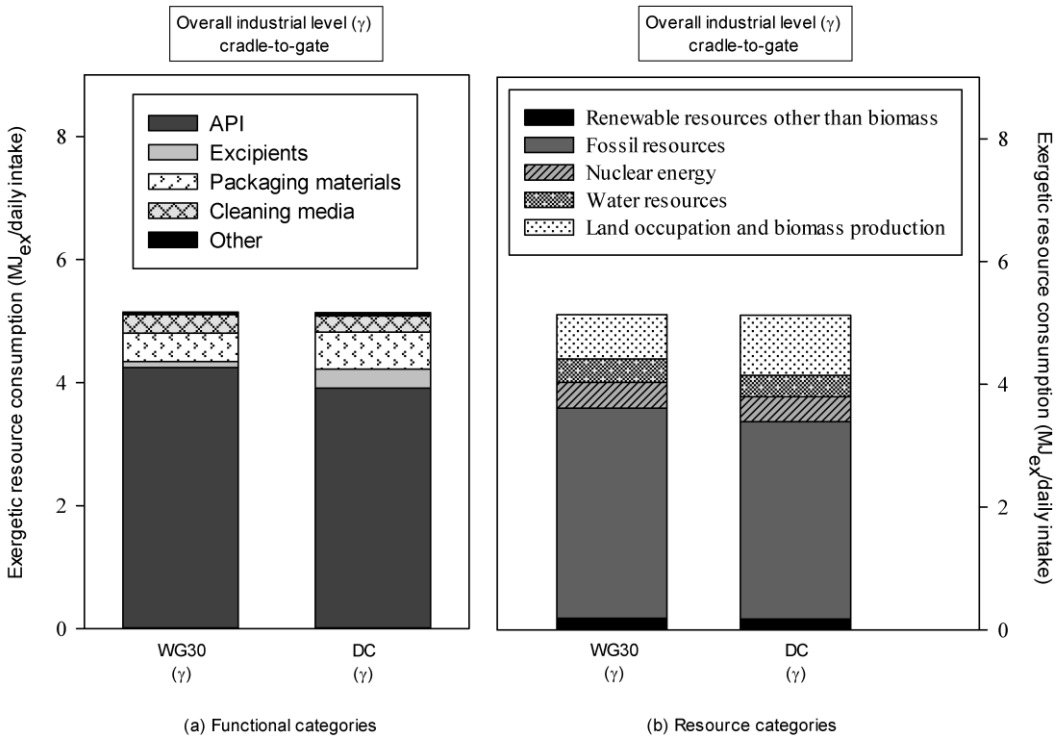

Figure 23: Cumulative exergetic resource consumption (MJ_{ex}/daily intake) of PREZISTA® 2 x 400 mg (Direct Compression, DC) and PREZISTA® 800 mg (Wet Granulation, WG30). Results are shown in functional categories (a) and resource categories (b) at overall industrial level (γ) (cradle-to-gate). The category 'other' includes the supply chains of electricity, heating media and compressed air. The results show a shift in relative contributions of resource categories to total resource extraction, but no significant difference occurs in absolute terms because of the trade-off between the extra granulation step in WG30 and the less efficient packaging phase in DC. (Note: categories 'metal ores' and 'minerals' in the CEENE footprint are not represented in this figure. In the case of pharmaceutical manufacturing, the latter contributions are to be neglected).

7.4 Conclusion

In this chapter the effect of scale-up (and learning) and tablet dosage (daily intake) on the cumulative resource extraction in the production of one daily dose of PREZISTA® was investigated. Overall, the effect of scale-up and learning on the resource consumption of Drug Product (DP) production proved to possess a power-law relationship $y = 2.40 * x^{-0.57}$ when shifting from smallest lab scale (WG1 = 1 kg/h) to industrial manufacturing (WG240 = 240 kg/h). The main message is twofold. First, deriving general trends in the experience curve of established technologies and its behaviour is a powerful backbone in the development of forecasting tools. This way, one can proactively include environmental indicators in R&D decision trees. Second, the author wants to stress the importance of taking into account R&D processes in assessing the environmental impact of products in an R&D intensive sector such as the pharmaceutical sector. Tablet dosage (2 x 400 mg tablets versus 1 x 800 mg tablet) did not significantly affect the environmental burden. The surplus of resources extracted due to the energy intensive granulation step in the production of the 800 mg tablet neutralizes the benefits of the more efficient packaging of the 800 mg tablet. It could be concluded that in meeting social and economic demands by launching the PREZISTA® 800 mg tablet, no trade-off in environmental burden occurred. On the long term, future research should strive to take into account R&D processes and all services related to pipeline activities taking place prior to market launch and eventually to allocate impacts to the final product.

Chapter 8
Forecasting and Streamlining: Simplification in Life Cycle Assessments

Redrafted from:

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8.1 Introduction

At an ever increasing rate innovative chemistry and technology platforms are reshaping pharmaceutical manufacturing environments to become real factories of the future as being more productive, lean and flexible (Crabtree, 2010; Bianchi et al., 2011; Rees, 2011). Within a global perspective, the streamlining of production supply chains tends to deliver complete treatments instead of isolated pharmaceuticals to meet customer demand (Bianchi et al., 2011; Rees, 2011). Whether or not this willingness to strive for innovation is a sustainable one can be evaluated using a wide range of assessment methods and indicators. With respect to the fine chemical and pharmaceutical industry, process oriented metrics such as Process Mass Intensity (PMI) and the E-factor are already known for a while, unlike life cycle based metrics which have been introduced occasionally in assessment methods adopted by big pharma (Jiménez-González, 2000; Jiménez-González et al., 2004a; Lapkin and Constable, 2009; Jimenez-Gonzalez et al., 2011). Various Life Cycle Assessments (LCAs) were conducted in primary and secondary pharmaceutical manufacturing comparing different types of chemistry and technologies to support decision makers (e.g. batch versus continuous pharmaceutical manufacturing) (Jiménez-González et al., 2004a; Dewulf et al., 2007b; Wernet et al., 2010; De Soete et al., 2013; Van der Vorst et al., 2013). Next to detailed case studies, generic tools were developed to assess the environmental sustainability of pharmaceutical products (Curzons et al., 2007; Van der Vorst et al., 2011). Testimony to this is for instance the streamlined life cycle assessment tool based on GlaxoSmithKline's FLASC™ tool (Fast Life Cycle Assessment of Synthetic Chemistry), developed by leading members of the American Chemical Society (ACS) Pharmaceutical Roundtable (PR) such as GSK, DSM and BMS (Curzons et al., 2007; Jiménez-González et al., 2013). Recent developments in the field of Product

Environmental Footprinting (PEF) and Product Category Rules (PCR) triggered a debate on how to assess the environmental sustainability of a company's product portfolio (European Commission, 2013). This led to a challenging discussion about assessing averaged product categories or product groups rather than single products in identifying hotspots and estimating the total environmental sustainability of one's product portfolio. By all means however, a case by case system comparison at any level of aggregation would be a complex, time-consuming task. A methodological framework in which forecasting models are used to predict environmental burden of products could be favourable to avoid time-consuming case studies. To facilitate the establishment of such a framework, correlation models between process parameters and environmental impact of products or product groups would be a first step. Formerly performed research by e.g. Wernet et al. already proved the dependency of some environmental impact categories on molecular structures (Finechem tool), however when supply chain data is accessible in an organization, readily available Enterprise Resource Planning (ERP) data on procurement, process operational variables (e.g. time, temperature, pressure), Bill of Materials (BOM), etc. could be integrated and would be a preferred way to derive the environmental impact of products and processes (Fischer and Hungerbuhler, 2000; Wernet et al., 2009). The author does acknowledge that in many organizations, additional efforts have to be made to reach this level of data management integration.

In the scope of the study performed in this chapter, the authors first examine the environmental sustainability of the production of five Active Pharmaceutical Ingredients (APIs), comprised of 40 different chemical synthesis steps in total (Table 9). With focus on cumulative resource extraction, results are reported at the overall industrial level (γ), taking into account the cradle-to-gate life cycle of the API (Figure 24). With the use of thermodynamic Life Cycle Analysis (LCA), process inefficiencies

are localized throughout the supply chain, identifying the hotspots of resource consumption. From a process engineering point of view, this is useful knowledge with respect to process optimization. The influence of the nature of deployed resources (e.g. building blocks, solvents, etc.) and used equipment on the integral resource consumption through the complete supply chain of API synthesis are highlighted, which in turn contributes to the created knowledge platform related to resource extraction during the synthesis of an API. This knowledge platform creation enabled the authors to propose justified parameters in the prediction of the real impact of API synthesis processes on our natural resource supply.

Subsequently, usefulness of correlation models is proven compared to averaged product groups as a simplification of LCA applications. Several predictor variables such as process operational parameters or simple process-oriented resource consumption indicators are used for the modelling of the cumulative resource consumption of chemical synthesis steps through the supply chain (γ). To find a justified balance in significant model complexity and embedded information on the one hand and usability, readily availability of data and capability of merging models with existing ERP data systems on the other hand, a set of five multiple linear regression models is proposed and evaluated.

8.2 Methodology

8.2.1 Hotspots identification

In order to arrive at an environmental sustainability assessment from a resource point of view of five Active Pharmaceutical Ingredients (APIs), first a qualitative analysis of 40 chemical synthesis steps was performed by studying 40 Batch Production Reports (BPRs), also known as the recipes, containing detailed process dependent data (e.g. time, temperature, pressure, etc.) of 2 839 Basic Operations (BOs) (e.g. cooling, heating, pumping, purging, etc.) (Table 9). For each chemical synthesis step, a BPR was available as illustrated in Figure 24 for Levocabastine production.

Table 9: Number of Batch Production Reports (BPRs) and Basic Operations (BOs) in the production of five Active Pharmaceutical Ingredients (APIs).

API	# BPRs	# BOs
(A) Domperidone	10	492
(B) Risperidone	7	502
(C) Ketoconazole	8	733
(D) Mitratapide	7	471
(E) Levocabastine	8	641

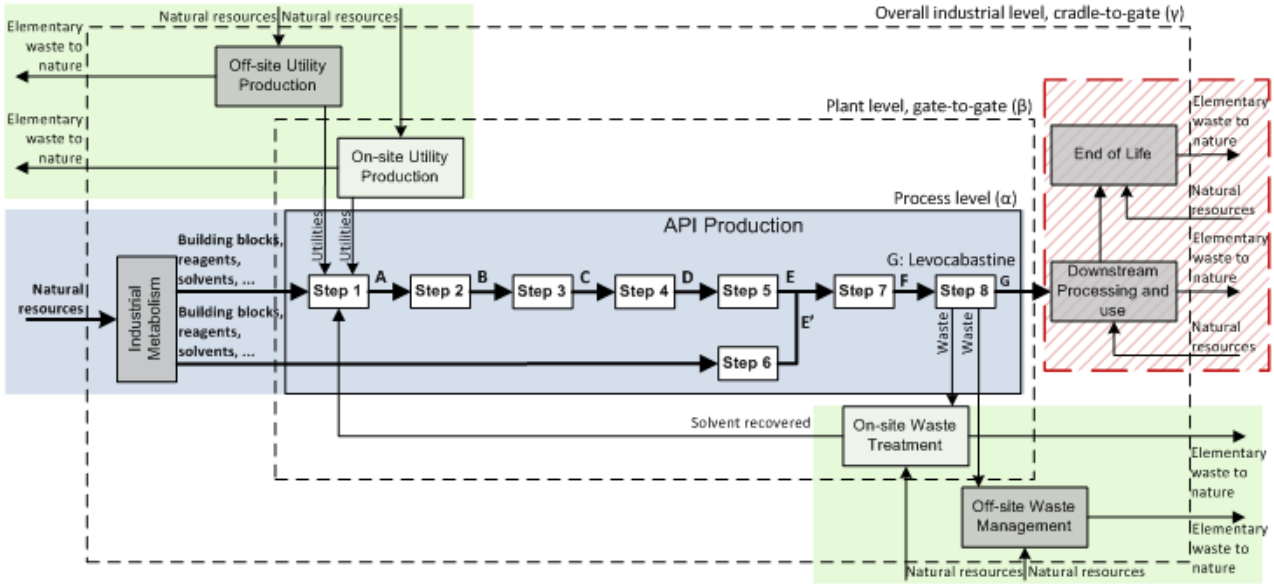

Figure 24: Simplified flowchart of Levocabastine production visualized within the three system boundaries of data inventory: process level (α), plant level (β) and overall industrial level (γ). Mind that in this study, the Active Pharmaceutical Ingredient (API) is the final product (flow G). Downstream processing into dosage forms (e.g. liquids), packaging, distribution, use phase and End-of-Life phase are not taken into account (red). The blue part indicates the core processes of the value stream and their upstream supply chain, while the green parts indicate utility production and waste treatment (downstream supply chain). These green indicated processes are supporting all synthesis steps, not merely step 1 and 8, as postulated in this flowchart as a matter of simplifying complexity.

At process level (α), quantification was performed by constructing mass and energy balances of each BO so as to map all inputs and outputs of a BO to its primary end product. For quantification at plant level (gate-to-gate, β) and overall industrial level (cradle-to-gate, γ), process data was coupled with a model to analyse integral resource consumption of individual chemical production processes in a multipurpose pharmaceutical production plant of Janssen Pharmarceutica NV, developed by Van der Vorst et al in 2009. The model takes into account all utilities (e.g. steam generation, compressed air production, etc.) and waste treatment facilities (e.g. waste water

treatment facility, distillation, etc.) needed to support the BOs at plant level (β) (Figure 24) (Van der Vorst et al., 2009a). Furthermore, it links back this on-site utility production and waste processing to industrial products and processes in the cradle-to-gate approach (γ) (e.g. natural gas to feed the steam generators), thereby coupling it with the ecoinvent v2.2 life cycle database, in order to create a complete Life Cycle Inventory (LCI) (Frischknecht and Rebitzer, 2005). Mind that what is called 'waste' and 'waste treatment' in this chapter is not necessarily reflecting the definitions of the EU Waste Framework Directive and its Flemish implementation (European Parliament, 19/11/2008). Waste is defined as any stream not contributing to the patient value of the final product, from a lean manufacturing point of view (Crabtree, 2010).

The Life Cycle Impact Assessment (LCIA) was done through Exergetic Life Cycle Impact Assessment (ELCIA) at the overall industrial or cradle-to-gate level (γ) (Szargut et al., 1988; Cornelissen, 1997; Cornelissen and Hirs, 2002; Dewulf and Van Langenhove, 2002; Dincer and Rosen, 2004; Szargut et al., 2005; Apaiah et al., 2006; Amini et al., 2007; Tsatsaronis, 2007; Dewulf et al., 2008; Dewulf et al., 2010; Herms, 2011). The Functional Unit (FU) is considered to be one mole of API. The indicator used is the Cumulative Exergy Extracted from the Natural Environment (CEENE) (De Meester et al., 2006; Dewulf et al., 2007a).

8.2.2 Simplification through multiple linear regression models

Based on the conducted case studies, a dataset with candidate predictor variables was constructed for which data of all 40 synthesis steps was inventoried at the Janssen Pharmaceutica NV full scale manufacturing plant in Geel, Belgium (Table 10). In order to predict the LOG (CEENE) of a pharmaceutical synthesis step, the Functional Unit (FU) is considered to be 1 mole of intermediate product. 15 variables were proposed, subdivided in four categories: (1) Process-oriented resource indicators; (2) Process operational parameters; (3) Equipment parameters and (4) Chemistry parameters. For this, Enterprise Resource Planning (ERP) systems, BPRs, equipment manuals, validation data, etc. were consulted.

Table 10: Dataset with candidate predictor variables for which data of all synthesis steps were inventoried. 15 variables were proposed, subdivided in four categories: (1) Process-oriented resource indicators; (2) Process operational parameters; (3) Equipment parameters and (4) Chemistry parameters.

Variable	Unit	Description
Process-oriented resource indicators		
Organic Solvent	L/mole	Total net(*) consumption of organic solvents in an intermediate synthesis step
PMI	kg/kg	Process Mass Intensity: $\frac{\text{Quantity of raw materials input of an intermediate synthesis step (kg)}}{\text{Quantity of product output from an intermediate synthesis step (kg)}}$
PMI*MW	kg/mole	Process Mass Intensity times Molecular Weight: $\frac{\text{Quantity of raw materials input of intermediate synthesis step (kg)}}{\text{Quantity of product output from an intermediate synthesis step (mole)}}$
Molar Efficiency	mole/mole	$\frac{\text{Output moles of product from an intermediate synthesis step (mole)}}{\text{Input moles of product of raw materials in an intermediate synthesis step (mole)}}$

Process operational parameters		
Δt	s/mole	Time duration of an intermediate synthesis step per mole output
ΔT	°C/mole	Absolute reaction mass temperature difference in an intermediate synthesis step per mole of output
Equipment parameters		
# Reactors	units/mole	Number of reactors used in an intermediate synthesis step per mole output
# Filters	units/mole	Number of filters used in an intermediate synthesis step per mole output
# Tanks	units/mole	Number of tanks used in an intermediate synthesis step per mole output
# Centrifuges	units/mole	Number of centrifuges used in an intermediate synthesis step per mole output
# Dryers	units/mole	Number of dryers used in an intermediate synthesis step per mole output
# Fixed equipment	units/mole	Σ(# Reactors, # Filters, # Tanks, # Centrifuges, # Dryers)
Chemistry parameters		
Addition	/mole	The value of this boolean parameter is equal to 1 if the dominant type of reaction in an intermediate synthesis step is an addition type of reaction. In all other cases, the value is equal to 0
Substitution	/mole	The value of this boolean parameter is equal to 1 if the dominant type of reaction in an intermediate synthesis step is a substitution type of reaction. In all other cases, the value is equal to 0
Elimination	/mole	The value of this boolean parameter is equal to 1 if the dominant type of reaction in an intermediate synthesis step is an elimination type of reaction. In all other cases, the value is equal to 0

(*) Total net consumption of organic solvents takes into account the amount of recuperated solvent through solvent recovery by distillation.

In building the multiple linear regression models, one predictor variable was eliminated each time in order to end up with a simplified linear regression with only one predictor

variable (backwards stepwise linear regression modelling) (Draper and Smith, 1981). For this, SPSS Statistics was used as a software package. Elimination of predictor variables was based on their significance ($p<0.05$), co-correlations between predictor variables and readily availability of data (Hocking, 1976). In order to evaluate models, the following selection criteria were proposed: (1) R^2 and (2) CI width. The squared residuals (R^2) or the determination coefficient is that fraction of the variance that can be clarified by the regression model while the width of the Confidence Interval (CI) is the averaged distance between the upper and lower boundary of the 95% confidence interval and is expressed in $kJ_{ex}/mole_{intermediate}$.

8.2.3 Simplification using the product group approach

In order to be able to compare the multiple linear regression approach with the product group approach, the average value of the LOG(CEENE) dataset was used. The correlation was evaluated comparing the R^2 of the constant average value with the R^2 of the different regression models.

8.3 Results and Discussion

Throughout the results and discussion chapter, the hotspots in resource consumption will be represented by means of seven functional categories: (1) chemicals; (2) electromechanical power; (3) heating media; (4) cooling media; (5) inert gasses (6) cleaning agents and (7) transport and treatment. Aforementioned resource categories do account for their supply and treatment or disposal as well (e.g. (1) production and use of chemicals, waste treatment and disposal). An additional and parallel subdivision of resource consumption will be provided according to the CEENE impact categories.

8.3.1 Hotspots identification

Out of the mass and energy balances at the overall industrial level (γ), Exergetic Life Cycle Impact Assessment (ELCIA) resulted in cumulative resource consumption data for the production of five Active Pharmaceutical Ingredients (APIs), comprising 40 synthesis steps. The total cumulative resource consumption proved to amount up to 4.3 ± 3.0 $GJ_{ex}/mole_{API}$, indicating a very wide spread between the five respective APIs. While the spread on the absolute cumulative resource consumption is rather high, Figure 25 explicitly indicates a recurrent pattern in the relative contribution of chemicals and their production on the one hand, and utilities and their production on the other hand. Chemicals showed to account for approximately 80% to cumulative resource consumption while utility production roughly consumes 20% of cumulative resource extraction in fine chemical and primary pharmaceutical production, confirming earlier findings in environmental sustainability assessments in the energy intensive pharmaceutical industry of e.g. (Wernet et al., 2010) and (Van der Vorst et al., 2011). For all that, this study provides a further breakdown of the contribution of chemicals to

the total cumulative resource extraction. Of all chemicals considered, the building blocks used in the beginning of the synthesis steps proved to be responsible for 22.5 ± 9.3%, whereas reagents proved to account for 10.2 ± 5.9%. Solvents showed to be the biggest contributor by far with 67.2 ± 12.7%, while catalysts showed almost no contribution to total resource extraction due to chemicals (0.1 ± 0.1%). The large spread on the contribution of chemical building blocks (which also induces a larger spread on reagents and solvent use) can be explained by unravelling the synthesis routes of the five APIs. Depending on the chemistry and the structure of the final API, some synthesis routes may start with relatively simple building blocks. More complex APIs may require rather complex building blocks from the overall industrial environment which causes their synthesis route at the pharmaceutical manufacturing plant not to start from scratch consequently. Out of Figure 25, which indicates the contribution to cumulative exergetic resource consumption through functional categories (%) in the production of (A) Domperidone; (B) Risperidone; (C) Ketoconazole; (D) Mitratapide and (E) Levocabastine at the overall industrial level (γ), it is clear that Levocabastine does not correspond to the 80%/20% rule of thumb that was proposed above. For that reason, the next paragraph specifies the production of Levocabastine in a more detailed way, in order to fully understand the striking difference with the other four cases.

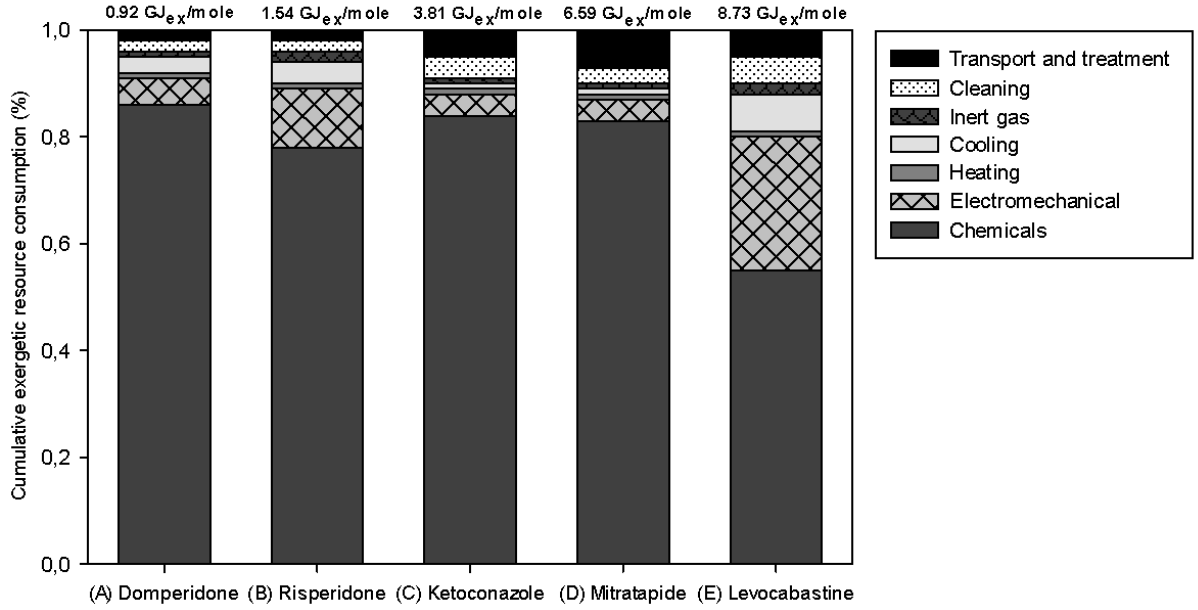

Figure 25: Contribution to cumulative exergetic resource consumption (%) in the production of (A) Domperidone, (B) Risperidone, (C) Ketoconazole, (D) Mitratapide and (E) Levocabastine at the overall industrial level (γ). The contribution to resource consumption is expressed in functional categories. Chemicals showed to account approximately for 80% to total resource consumption while utility production roughly consumes 20% of resource extraction in fine chemical and primary pharmaceutical production. Exception within these five cases is Levocabastine with its high demand for electromechanical resources due to extensive drying operations in step 5, 7 and 8.

8.3.2 The case of Levocabastine

With 8.73 $GJ_{ex}/mole_{API}$, Levocabastine showed to be the highest contributor of all cases to the cumulative exergetic resource extraction, but it also proved to possess a remarkable difference in relative contributions. Unmistakable was the hotspot contribution of electromechanical resources (2.14 $GJ_{ex}/mole_{API}$). Looking back to the Basic Operations (BOs) occurring in the respective synthesis steps of Levocabastine (Figure 24) revealed the physical origin behind this result. While step 4 is most favourable in terms of thermodynamics, step 5, 7 and 8 show significant electromechanical exergy consumption due to extensive mixture stirring and subsequent drying operations. In total, more than 50 hours of drying at 70°C demand power consumption to pump drying air and to stir the wet powder. The long duration (predictor variable Δt) of these BOs causes the electromechanical resources to contribute to a higher extent to total resource consumption compared to the other cases. The findings on the relevance of process oriented parameters (e.g. Δt) and equipment parameters contributed to the establishment of the set of candidate predictors in the multiple regression modelling as well. From another point of view, the resource footprint (according to the relevant CEENE categories) was investigated and related to the high demand for electrometrical resources. Figure 26 shows the cumulative exergetic resource consumption ($GJ_{ex}/mole_{intermediate}$) through the eight step synthesis pathway of Levocabastine. Bearing in mind that the green electricity mix used at the manufacturing site of Janssen Pharmaceutica NV in Geel was taken into account as a background utility in the used model of Van der Vorst et al., Figure 26 clearly relates the high demand for electromechanical resources in step 5, 7 and 8 to an increased demand of land occupation, biomass production and fossil resources at the cradle of resource extraction. As a result, aforementioned resource categories showed to be the most important hotspots in the cumulative resource consumption of the full synthesis pathway of

Levocabastine (Figure 26). Mind that synthesis step 6 is performed parallel to the linear route of step 1 to 5, as became clear out of Figure 24. In step 7, the CEENE of both routes and extra resources used in synthesis step 7 adds up to the total CEENE of this step.

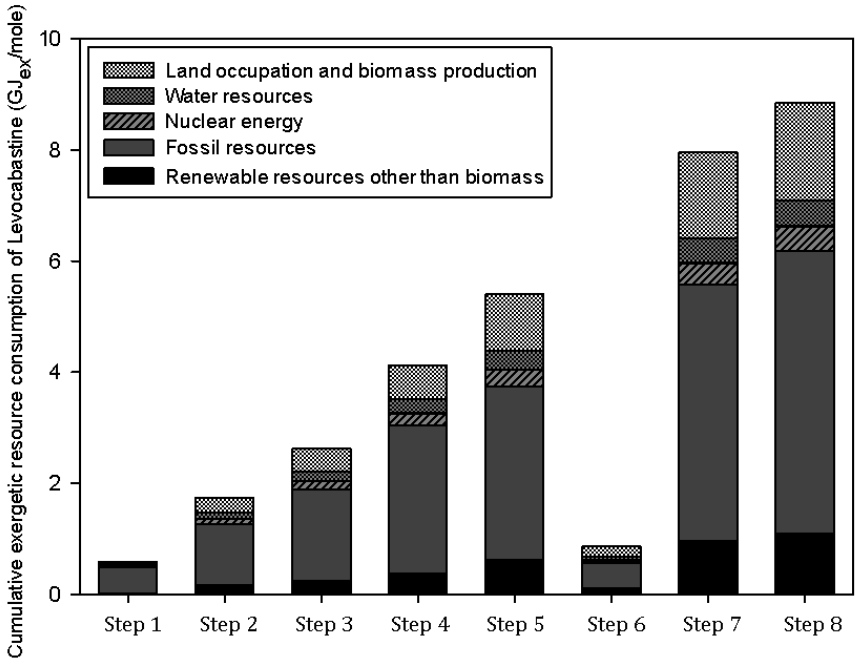

Figure 26: Cumulative exergetic resource consumption ($GJ_{ex}/mole_{intermediate}$) through the eight step synthesis pathway of Levocabastine. Contribution to resource consumption is expressed according to the relevant CEENE categories. This figure clearly relates the high demand for electromechanical resources in step 5, 7 and 8 to an increased demand of land occupation, biomass production and fossil resources at the cradle of resource extraction.

To conclude, it was observed that there was little variance in the relative contributions of functional categories to total cumulative resource extraction. Except for Levocabastine, the results were in line with earlier statements of (Wernet et al., 2010). On the contrary, the spread on the absolute values of cumulative resource extraction proved to be considerably large (4.3 ± 3.0 $GJ_{ex}/mole_{API}$). With a factor 10 difference in absolute cumulative resource extraction, it makes no sense to use product groups as an estimation of the impact of a certain product. Out of these findings the emergence

arouses to construct correlation models to estimate the absolute cumulative resource consumption through the complete supply chain (γ) to a better extent than just with an average value of product groups.

8.3.3 Simplification through multiple linear regression models

The results obtained from the above mentioned case studies reveal the need for a pharmaceutical company to assess the order of magnitude of their cumulative resource consumption (γ), rather than the relative contribution of different sources (which is reasonably of the same order of magnitude). This can be done by introducing an average value for product categories or through forecasting modelling. In order to select appropriate predictor variables to be used in the multiple linear regression models, the following line of thought was pursued. First, all candidate predictors where tested on their distribution (Mosteller and Tukey, 1977). To assure the normal distribution of candidate predictors, logistic or square root transformations were performed according to the nature of the original Poisson distribution of the candidate predictors (Mosteller and Tukey, 1977; Weisberg, 1980; Huijbregts et al., 2010). Next, single regressions of all 15 single predictor variables were computed to test which parameters could best estimate the response variable Cumulative Exergy Extracted from the Natural Environment LOG(CEENE) of a pharmaceutical synthesis step. Figure 27 shows that process-oriented resource indicators, process operational parameters and the number of reactors used in a synthesis step (n = 40) proved to be good predictors of the LOG(CEENE). Chemistry parameters showed no correlation at all since they were defined as boolean parameter assigning a value of 1 to the most dominant type of reaction only. It should be said that a similar correlation could be established for other life cycle impact categories as well such as climate change or ozone depletion.

Huijbregts et al. established relationships between straightforward resource oriented indicators (e.g. Cumulative Energy Demand) and indicators within other impact categories (e.g. CO_2-eq or Ozone Depletion Potential) for a wide range of products (Huijbregts et al., 2010). Based on the correlation coefficients in Figure 27, the acquired knowledge from identifying aforementioned hotspots in several case studies and potential readily availability of data through Enterprise Resource Planning (ERP) systems (e.g. organic solvent use versus PMI), five predictor variables were selected out of different subcategories so as to construct the five multiple linear regression models: (1) Organic Solvent; (2) Molar Efficiency; (3) Δt; (4) ΔT and (5) # Reactors (Figure 27).

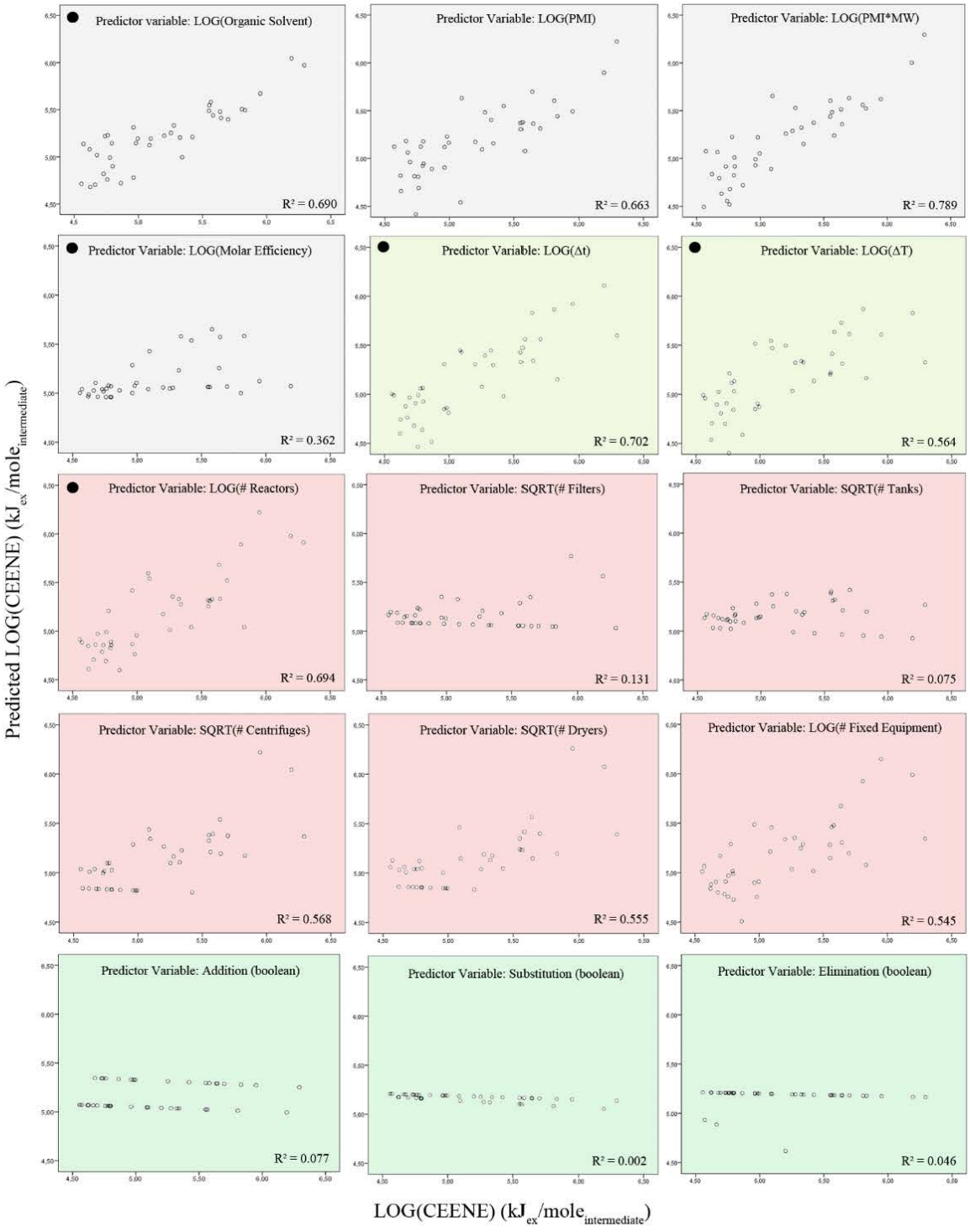
Predictor variable: LOG(Organic Solvent)
R² = 0.690
Predictor Variable: LOG(PMI)
R² = 0.663
Predictor Variable: LOG(PMI*MW)
R² = 0.789
Predictor Variable: LOG(Molar Efficiency)
R² = 0.362
Predictor Variable: LOG(Δt)
R² = 0.702
Predictor Variable: LOG(ΔT)
R² = 0.564
Predictor Variable: LOG(# Reactors)
R² = 0.694
Predictor Variable: SQRT(# Filters)
R² = 0.131
Predictor Variable: SQRT(# Tanks)
R² = 0.075
Predictor Variable: SQRT(# Centrifuges)
R² = 0.568
Predictor Variable: SQRT(# Dryers)
R² = 0.555
Predictor Variable: LOG(# Fixed Equipment)
R² = 0.545
Predictor Variable: Addition (boolean)
R² = 0.077
Predictor Variable: Substitution (boolean)
R² = 0.002
Predictor Variable: Elimination (boolean)
R² = 0.046
Predicted LOG(CEENE) (kJ_ex/mole_intermediate)
LOG(CEENE) (kJ_ex/mole_intermediate)

Figure 27: Linear correlation of LOG(CEENE) of a pharmaceutical synthesis step (n = 40) with 15 predictor variables, subdivided in four categories: (1) Process-oriented resource indicators (grey); (2) Process operational parameters (light green); (3) Equipment parameters (pink) and (4) Chemistry parameters (green). Process-oriented resource indicators, process operational parameters and the number of reactors used in a synthesis step proved to be good predictors of the LOG(CEENE). Chemistry parameters showed no correlation at all. Five predictor variables were selected: (1) Organic Solvent; (2) Molar Efficiency; (3) Δt; (4) ΔT and (5) # Reactors

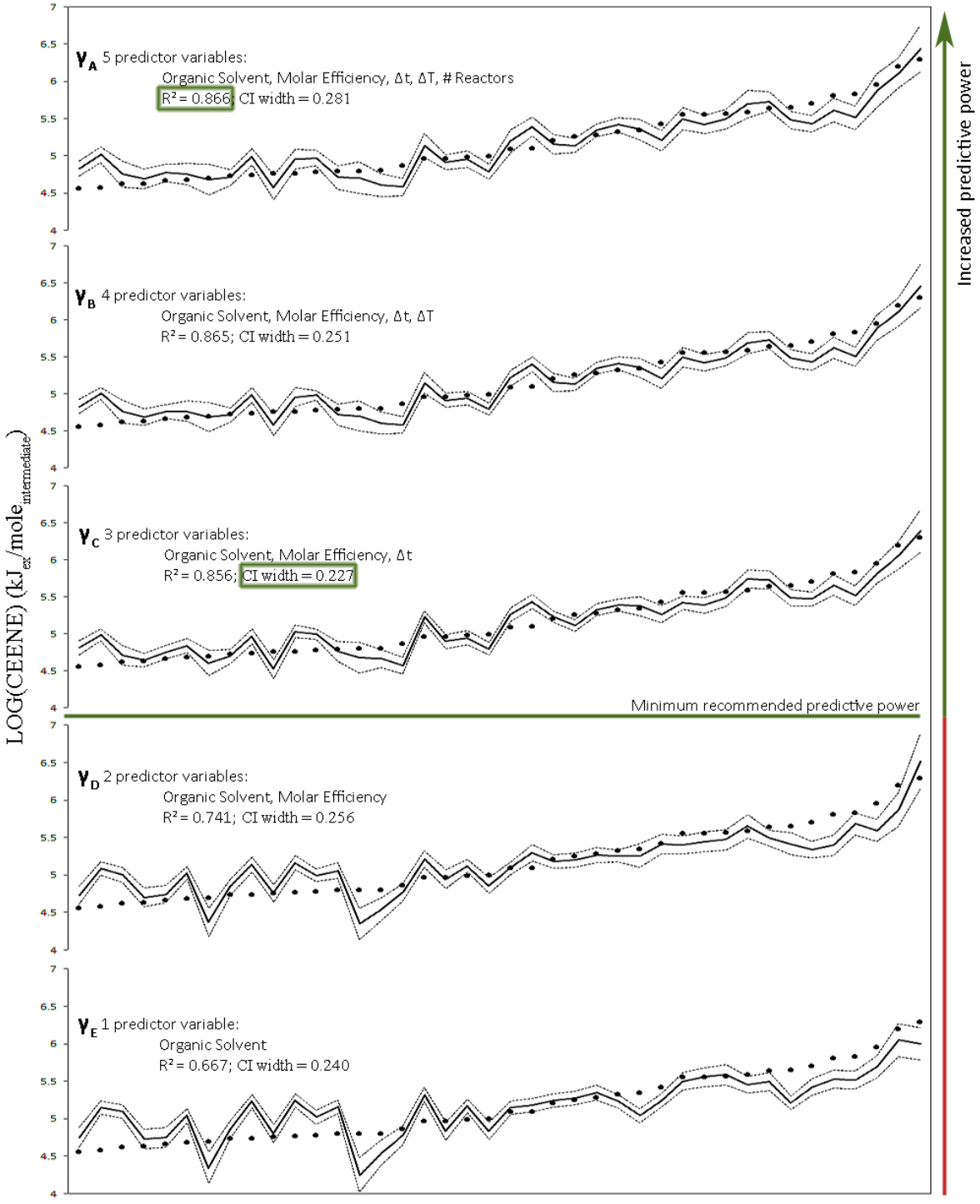

Figure 28: Model construction procedure (models γ_A, γ_B, γ_C, γ_D, γ_E). • indicates the logarithm of the calculated LOG(CEENE) ($kJ_{ex}/mole_{intermediate}$) values for all 40 synthesis steps, ─ is the model prediction of LOG(CEENE) ($kJ_{ex}/mole_{intermediate}$) for the corresponding steps while ··· represents the 95% confidence interval ($kJ_{ex}/mole_{intermediate}$) (n = 40, sorted by increased impact).

Figure 28 represents the construction procedure of the five regression models. The first model, model γ_A includes the complete set of five response variables. For every subsequent model (indicated by subscripts B, C, D and E), one predictor variable was eliminated from the multiple regression model (according to the procedure described in materials and methods, Chapter 8.2.2) so as to finally end up with a regression with only one predictor variable.

(29)

$$LOG(CEENE_A) = 3.575 + 0.269 * LOG(Organic\ Solvent) - 0.693 * LOG(Molar\ Efficiency) + 0.550 * LOG(\Delta t) - 0.201 * LOG(\Delta T) - 0.043 * LOG(\#\ Reactors)$$

Evaluating model γ_A, prediction variables ΔT and # Reactors showed no significant contribution to the prediction of $CEENE_A$ ($p = 0.13$ and 0.79 respectively) and proved to be correlated strongly. Moreover their model parameters showed the opposite sign of what one would have expected, as a higher ΔT and a higher # Reactors would result in a higher cumulative resource demand. Eliminating these two predictor variables resulted in model γ_C:

(30)

$$LOG(CEENE_C) = 4.280 + 0.266 * LOG(Organic\ Solvent) - 0.709 * LOG(Molar\ Efficiency) + 0.328 * LOG(\Delta t)$$

With just a slight decrease in R^2 (0.856 versus 0.866) model γ_C showed to be slightly more reliable in terms of precision and accuracy than model γ_A. Due to a lower

uncertainty in predictor variables, the width of the confidence interval proved to be smaller (0.227 versus 0.281 $kJ_{ex}/mole_{intermediate}$). As can be seen in Table 11, further elimination of predictor variables caused models γ_D and γ_E to lose their predictive power to a large extent. In case only the use of organic solvent was included, the R^2 decreased to 0.667 and the confidence interval expanded to a width of 0.240 $kJ_{ex}/mole_{intermediate}$ (model γ_E):

$$LOG(CEENE_E) = 5.032 + 0.648 * LOG(Organic\ Solvent) \quad (31)$$

This would suggest that a model with three predictor variables (Organic Solvent, Molar Efficiency and Δt) would be helpful to provide more intuitive understanding and to unravel the physical relationships between simple process-oriented resource indicators such as Organic Solvent use and Molar Efficiency and process operational parameters such as Δt on the one hand and the cumulative resource consumption of an API synthesis step on the other hand. For the reader's interest, all proposed models can be found in Annex A6. Based on the availability of data and the desired accuracy and precision, the practitioner may select the most favourable model. Table 11 shows the scores on the selection criteria of each correlation.

Table 11: Resource consumption correlation models and scores on their selection criteria.

Model	Predictor variables	R^2	CI width (kJ_{ex}/ $mole_{intermediate}$)
Response variable = LOG(CEENE)			
γ_A	Organic Solvent, Molar Efficiency, Δt, ΔT, # Reactors	0.866	0.281
γ_B	Organic Solvent, Molar Efficiency, Δt, ΔT	0.865	0.251
γ_C	Organic Solvent, Molar Efficiency, Δt	0.856	0.227
γ_D	Organic Solvent, Molar Efficiency	0.741	0.256

γ_E	Organic Solvent	0.667	0.240

8.3.4 Simplification using the product group approach

The previous paragraph evaluated the predictive power of the five proposed multiple linear regression models with the criteria described in the materials and methods section. Model γ_E showed the worst scores on all criteria. Nevertheless, no matter what model was used, all models showed a better correlation with LOG(CEENE) than the mean of the dataset which equals 5.167 $kJ_{ex}/mole_{intermediate}$ (R^2 = 3.40E-30) and represents the product group. One can imagine the product group average to be a horizontal curve at LOG(CEENE) = 5.167 in Figure 28.

8.3.5 Multiple linear regression model development: optimal degree of complexity?

Whereas in literature, the use of organic solvents or the Process Mass Intensity (PMI) were postulated to be good estimates of the cumulative resource consumption of an Active Pharmaceutical Ingredient (API) synthesis step, the correlation can be optimized to a large extent and be more reliable upon inclusion of two more parameters (Δt and Molar Efficiency). Depending on the availability of data in one's organizational ERP system, the practitioner can apply one of the models taking into account the reported underlying uncertainty. The authors advise to use at least three predictor variables whenever possible since models with less predictors score significantly worse on all model selection criteria. Including additional predictor variables might in some cases be an unnecessary, time-consuming and complicated task which may not benefit the predictive character and can eventually weaken the interpretation of such a model. The

correlation models proposed in this chapter can and will be used in other cases to be validated for prediction. In future, ideally, an organization should be able to derive the environmental impact of its portfolio from enterprise resource data, linking supply chains back to the cradle of resource extraction. This study has taken a step in that direction with a strong statement in the discussion of environmental sustainability assessment of product groups rather than assessing the real impact of one's product portfolio with available enterprise resource data. The author acknowledges that the latter might not be an easy task but it definitely yields a more reliable approach than the product group method. The regression formulas are currently adopted by the UK's NHS Sustainable Development Unit (SDU) in their report on how to calculate and communicate environmental impacts of pharmaceuticals (NHS Sustainable Development Unit, 2012).

Chapter 9
An Emerging Need to Integrate Life Cycle Management within Business Operational Management Tools

Redrafted from:

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9.1 Introduction

When Goldratt first introduced his Theory of Constraints (ToC) in The Goal (1984) and The Critical Chain (1997), he did not only refer to manufacturing Value Chains (VCs) sending the boy scouts on the narrow forest trail (Goldratt, 1997; Goldratt and Cox, 2014). A metaphoric way of debottlenecking that found its way in various types of management, from office management to business management, from visual management on the floor to the most advanced planning systems. A few decades before, yet another great scientist called Dennis Meadows published his severe concerns on exponential growth due to the industrialism and a limited supply of resources (Meadows and Meadows, 2007). At first glance, striving towards higher efficiencies and economic growth evermore would be in contrast with Meadows' Limits to Growth. However, under the Malthusian ceiling, intensification in processing industries is all about doing more with less (Malthus, 1798; Dewulf et al., 2000; Dewulf et al., 2010). Whether it was Thomas Malthus, Dennis Meadows or Eliyahu Goldratt that pulled the strings, they all shared a complementary vision towards sustainment and sustainability.

Sustainable development in its broadest sense could possibly best be described as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs", suggested by Brundtland and the World Commission on Environment and Development (WCED) (Brundtland, 1987). The aforementioned definition lacks a comprehensive description of 'needs'. From an individual or microeconomic perspective, we could reflect the needs of a human being to the Maslov Hierarchy and the utility of that human being given to a certain attribute of a product or service (Kainuma and Tawara, 2006). However, from a societal point of view, sustainability professionals often subdivide between economic prosperity,

environmental sustainability and social sustainability (the triple bottom line) (Elkington, 1998; Taormina and Gao, 2013).

Next to sustainability and sustainable development, sustainment is key in quantifying, monitoring and eventually maintaining our efforts towards sustainable development, continuous improvement, Operational Excellence, etc. Measuring performance (prosperity, environmental sustainability and social sustainability) is of utmost importance to evaluate continuous improvement actions or eco-design alternatives in early R&D development stages. A widely used methodology to assess sustainability is Life Cycle Sustainability Assessment (LCSA), reaching out to economic prosperity (Life Cycle Costing, LCC), environmental LCA and social aspects through SLCA. Environmental LCA has extensively been used since the past decade to assess whether or not a (established, enabling or prospective) technology or product is environmentally sustainable, to perform eco-design, for sustainability reporting, to comply with NGO requests, but above all for internal process optimisation (Van der Vorst et al., 2009b; De Soete et al., 2013; Jiménez-González et al., 2013; De Soete et al., 2014a; De Soete et al., 2014b; Jimenez-Gonzalez and Overcash, 2014; Cespi et al., 2015; Kralisch et al., 2015). To this extent it overlaps strongly with the field of Operational Excellence (OE) and the Lean heritage. Until now, the link between ICT tools for Operational Excellence or Business Administration (BA) in general is hardly connected to the data-intensive process modelling software such as ASPEN® or LCA software such as Simapro or OpenLCA.

Several studies, regulations and European Directives have shown the need for a more efficient way to perform LCA through value chains (Cespi et al., 2015; European Commission, 2015b; Passer et al., 2015). As an example, Environmental Product

Declarations (EPDs) are becoming mandatory for all building materials within the construction sector (Passer et al., 2015). An EPD is a standardised type of report from an LCA. This means that for every building material sold on the market, an LCA has to be conducted, nearly impossible without a certain degree of automation. Together with the European Centre of Innovation and Technology (EIT) and the EIT on Raw Materials, the Digital Agenda (DA) and the Internet of Things (IoT), the European Commission sets objectives for the growth of the European Union (EU) by 2020 (ISA, 2015). The DA proposes to better exploit the potential of Information and Communication Technologies (ICTs) in order to foster innovation, economic growth and progress. With a strong policy driven focus, the emergence of more efficient LCA methodologies and their use cases are obviously present. Of interest to the reader, other examples are the European Plastics Federation (PlasticsEurope), the Green Procurement Initiative of the United Nations Development Program (UNDP), etc. The next paragraph will elaborate on the possible bottlenecks in integrating such a system as described above, how we can overcome this urge and what are the clear wins towards fully integrating these systems.

9.2 Potential bottlenecks in the integration of process modelling and Enterprise Resource Planning (ERP) Systems

9.2.1 Data management in organizations

Depending on the type and scale of organisation, the sector to which it delivers products and services and its stakeholders, organisational data is structured in business IT and ICT tools and systems. In the processing industry, the horizontal structure of an organisation (Production, Planning, Finance, Legal Affairs, Procurement, HR, EHS&S, QA/QC, Engineering, Validation, etc.) stores thousands of terabytes (or pages) creating a data-dependent structure in need of smart and consistent logging systems. Some of them are integrated in so-called Enterprise Resource Planning (ERP) systems, such as SAP and Infor LN. ERP systems are used for a variety of applications as shown in Figure 29, which can potentially be subdivided in four categories: (1) Business Intelligence; (2) Enterprise Management; (3) Commercial Applications and (4) Customised ERP Systems or modules. A widespread example is production planning, which can be based on forecasting, stock levels (push production), a planning rhythm wheel, etc. Whenever the market is saturated or is characterised by a stable demand, push production is often applied. A Manufacturing Resource Planning (MRP) system steers the production based on stock levels and will send orders to suppliers to replenish in-house stock levels.

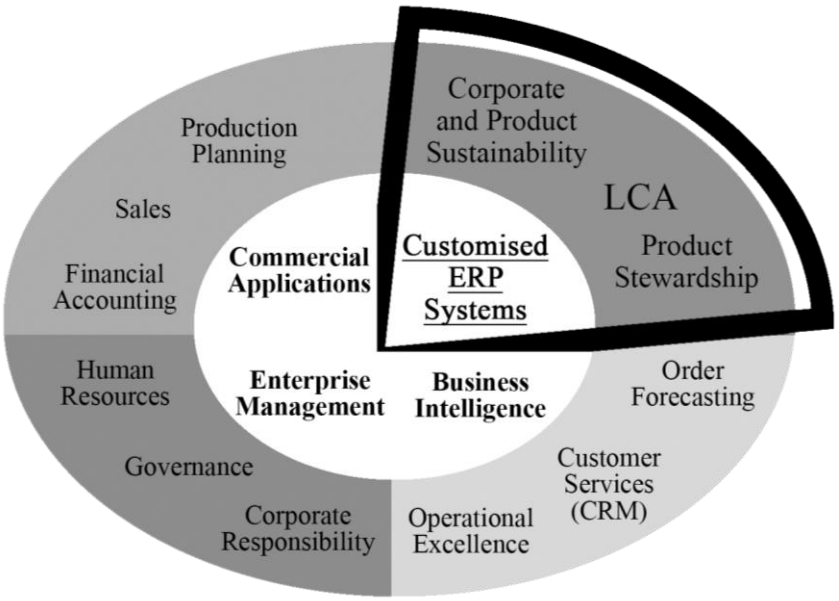

Figure 29: ERP systems are used for a variety of applications, which can potentially be subdivided in four categories: (1) Business Intelligence; (2) Enterprise Management; (3) Commercial Applications and (4) Customised ERP Systems or modules. A widespread example is production planning, which can be based on forecasting, stock levels (push production), a planning rhythm wheel, etc.

An ERP system is generally custom configured for a certain enterprise. The customised applications of resource planning systems are endless (Res et al., 2011). Such customised applications might ease the daily operations of e.g. warehouse management (efficient order pick-up, standardised work, etc.).

The introduction of this chapter touched upon the similarity between Lean and sustainable manufacturing, between the visions of Goldratt, Malthus and Meadows. Product and organisational sustainability could be quantified using organisational operational data in a customised ERP module, as has been proposed by De Soete et al., 2014b. The authors provide correlations (see Chapter 8 and Annex 6) between the as candidate predictor variables. Ideally, through machine learning, these correlations can

be optimised in a customised module. Further elaboration on the feasibility of new frameworks is given in chapter 9.3: Proposed pathways for integration. The subchapters below describe some of the bottlenecks in relying on ERP data and in the integration of tools for corporate and product sustainability assessments. Related to Figure 29 one should take into account these bottlenecks in building customised ERP modules.

9.2.2 Data penetration through MES

Production line sensors, logging systems or Supervisory Control And Data Acquisition (SCADA) systems are connected with the ERP systems for the different business departments to work with through the so-called Manufacturing Execution System (MES). The MES could be described as the interface between the plant floor (Gemba) and the ERP system. Possible applications of MES are automated equipment, maintenance support and process control (Li et al., 2012). Data from particular sensors (e.g. temperature sensors, level sensors, flow rate sensors, product homogeneity through NIR etc.) that have no direct use in any ERP module might not penetrate through the MES layer (e.g. for process control). These types of data are essential in sustainability assessments and LCA in general to construct mass and energy balances of the production in scope of the analysis. Without modifications on the data submission path to customised ERP systems, integrating organisational and product sustainability in ERP modules for EHS&S and Product Stewardship is challenging. It will reduce the data quality of the LCA and will require more modelling in the end (e.g. through machine learning) instead of using primary data.

9.2.3 Consistency in data feeding/logging

Following on De Soete et. al. (2014) a feasibility study was performed on using different ERP data in forecasting methods for the environmental sustainability of products, as postulated in the previous subchapter. The lack of consistency in data feeding into ERP systems from e.g. operator entries on waste, solvent use, etc. was perceived to be a bottleneck. The use of different units for one and the same physical-chemical variable is another bottleneck to get to work on. A proposed way to deal with these inconsistencies is the proper use of Standard Operating Procedures (SOPs) and sustainment through properly defined Key Performance Indicators (KPIs). These management tools are widely used through organisations to foster consistency and to reduce variability in production environments leading to increased lead times. However, the application of these tools should be more horizontally integrated in order to strive for an effective and efficient usage.

9.2.4 Supply Chain transparency

Once a comprehensive data system is sustained in an ERP system, Supply Chain (SC) transparency becomes a key issue to guarantee data quality and visibility into the extended SC. Moreover, it protects any processing company against supply disruptions and unbalanced replenishment. In general, it reduces supply risk effectively. Transparency will become more and more a key issue in global SCs and will further develop as it turns out to be crucial for wider social developments such as globalization, the information age, and the shifting role of states in environmental governance. Transparency in SCs is bound up with positive connotations: the more transparency the better it is for the sustainability of chains and for the empowerment of one's consumers (Mol, 2015). Thus also for customised ERP modules for e.g. sustainability assessments,

internal SC data management and external SC interfacing, confidentiality issues in data transparency of suppliers, etc. are potential risks or bottlenecks to be monitored and tackled.

9.2.5 Supply Chain reliability

Nevertheless, transparency can only be guaranteed if the supply of raw materials through the Supply Chain (SC) is stable and a certain level of business continuity has been reached. The importance of business continuity plans is well recognized by organizations all over the world that are increasingly operating in a global, complex and competitive environment. Their core business and SCs can easily be interrupted by economic, social, political, technical and environment related unforeseen events. Natural disasters, diseases, financial crises, unreliable supply chains leading to disruptions and many more can severely impact growth and performance (Faertes, 2015). The work of Cheung et. al. (2014) revealed a paradigm shift in which data generated by manufacturers within the process industries identify failures which they are introducing into the SC (Cheung et al., 2014). This means that transparency and reliability are strongly related and a consistent use of data is key to enhance performance and avoid disruptions. As a leading example, the pharmaceutical and medical device industries are developing Good Supply Practices (GSPs), next to the Good Manufacturing Practices (GMP) required by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) in order to foster reliability through the SC (Cheung et al., 2014). Despite all, supply disruptions are surely enough all too common. To mitigate delivery risk, buyers may either source from multiple suppliers or offer benefits to preferred suppliers to improve SC reliability (Tang et al., 2014). These incentives towards suppliers can either be direct (investment subsidy) or indirect

(inflated order quantity). Preferably a mixed model of investment subsidy and/or inflated order quantity for the preferred supplier together with multiple supplier sourcing as alternative delivery in case of partial disruption is applied (Tang et al., 2014).

It is not hard to imagine that if the physical supply of goods or the delivery of services cannot be guaranteed, the penetration of SC data and process data of n-x suppliers to end producers is all but apparent. Even though the supply would theoretically be completely secured, companies might be resistant to data sharing in order to preserve their competitive advantage in the global environment (De Soete et al., 2014b). However, well considered business models can ensure process data sharing with a certain degree of aggregation and black box modelling throughout the SC to enhance the use of primary process data of suppliers for e.g. sustainability assessments through Life Cycle Assessment (LCA). These data sharing models with care for business integrity and confidentiality has the power to lead to shared value through the SC, since LCA can indicate priorities for optimisation and resource consumption reduction for all n-x suppliers. If the model fails to deliver reliable data, it might be better to use secondary (averaged) market data as proxy values to reduce data uncertainty of the LCA results. Nonetheless, one should strive for connecting suppliers as much as possible and enhance the use of primary data to create shared value approaches and facilitate assessment of product and corporate sustainability in general.

9.2.6 Different languages

Next to data penetration, consistency, transparency and reliability, another bottleneck in this non-exclusive list is related to the programming and interfacing of different data formats to perform sustainability assessments. While correlation models of processing

data with environmental data can be made with R, SPSS or any program for statistical analysis, Life Cycle Inventory (LCI) database exchange formats are commonly working with extensions such as .xml (extended mark-up language, such as in the ecospold formatting), .oLCA (OpenLCA database format) etc. (Ciroth et al., 2013; De Soete et al., 2014b). To convert LCI databases to work with in different software packages, the so-called OpenLCA format converter was developed by GreenDelta GmbH (Ciroth et al., 2013). However, engineering modelling software such as ASPEN and LCI databases do not speak the same language. Therefore, interfacing different types of data is still to be considered a potential bottleneck in connecting aforementioned modules in MES or ERP systems.

9.3 Proposed pathways for integration

9.3.1 A common framework

The previous chapter highlighted some of the most abundant bottlenecks experienced in implementing sustainability assessments through Life Cycle Assessment (LCA), related to operational management within manufacturing and Supply Chain (SC) environments. Figure 30 illustrates a highly simplified integration of IT/ICT tools in manufacturing environments, where several layers can be distinguished (Schmidtmann et al., 2009; Hanel and Felden, 2011). Bearing in mind the tools and principle heritage of Lean Manufacturing and Six Sigma Management, everything starts at the Plant Floor or 'Gemba', the place where value is essentially created (Bicheno and Holweg, 2009; Crabtree, 2010; Wilson, 2010; Liker and Convis, 2012). On the Floor, the bottom up construction of data systems starts with sensors based on all kinds of technologies (volume sensors, mass sensors, structure sensors, temperature sensors etc.). Most of these sensors send data signals at predefined intervals to logging systems such as Supervisory Control And Data Acquisition (SCADA) systems. Some process variables such as timings are inserted as queries through an Operator Interface (e.g. provided by Siemens) to be used in the construction of Batch Production Reports (BPRs) etc. The measured data is send to the next layer in the programming structure, being the Manufacturing Execution System (MES). In the MES, process data coming from the Floor is being used to create BPRs, calculate performance indicators such as the Overall Equipment Effectiveness (OEE), regulate process control systems and many more. The manufacturing data systems are connected to the corporate enterprise systems. The third

layer in the framework is the Enterprise Resource Planning (ERP) system. This third layer allows enterprises to manage their resources from both a top down (production planning) and a bottom up (replenishment) approach. From NGOs, policy makers, end-users and the whole stakeholder communities, questions arise on whether or not this supply chain and manufacturing is sustainable and safe. When it comes to product and organizational sustainability for purposes of Product Environmental Footprinting (PEF), Green Procurement and Product Stewardship, data seems to be lacking in order to conduct sustainability assessments proficiently. Years of intensive research by means of backwards stepwise linear regression modelling and experience proved that primary data to perform sustainability assessments often are measured through equipment control sensors (e.g. flow rates, temperatures, concentrations, pressures etc.) and sent to PLCs and many other systems (De Soete et al., 2014b). Nevertheless, these engineering data measurements are in many cases simply not penetrating through the Manufacturing Execution Systems (MES) because they seem to be of little value for existing ERP applications.

An ERP system is generally customised for a certain enterprise. The customised applications of resource planning systems can be adjusted to the needs of an organisation. Correlation models between process data (e.g. temperature, mass yield, organic solvent use) and environmental sustainability performance (e.g. cumulative resource consumption, carbon emissions, etc.) that were found by De Soete et. al. (2014) and adopted by the Sustainable Development Unit (SDU) of the British National Health Service (NHS) were tested on their feasibility to be integrated in customised ERP

applications (De Soete et al., 2014b; Penny et al., 2015). It was proven that by combining MES data from batch reports (e.g. time duration of a chemical synthesis step), line sensors (e.g. operating temperatures), Bill Of Materials (BOM) (e.g. raw material use), indicators for environmental sustainability could be derived (e.g. Cumulative Exergy Extracted from the Natural Environment, CEENE and the Carbon Footprint, CF) (Dewulf et al., 2007a; Weidema et al., 2008; Wiedmann, 2009; Lenzen et al., 2010; Van der Vorst et al., 2011; Alvarenga et al., 2013; Taelman et al., 2014). Ideally, these aforementioned correlations, engineering modules, design software such as ASPEN are to be built in in a customised ERP application for LCA (as visualised in Figure 30) in order to couple primary engineering data, Life Cycle Inventory databases (LCI, e.g. ecoinvent) and Life Cycle Impact Assessment Methods (LCIAM, such as CEENE and CF). The role of these different configurations and to what extent they can be automated to generate a 'life footprint' will be elaborated in chapter 9.3.2. With the construction of customised ERP modules for automated sustainability assessments, corporate and product sustainability can be quantified to be used for several applications: Corporate Sustainability Reporting (CSR), continuous improvement actions within the organisation, marketing, B2B and B2C communications, etc. Ideally, such a system should be sustained by the top management by means of e.g. Key Performance Indicators (KPIs).

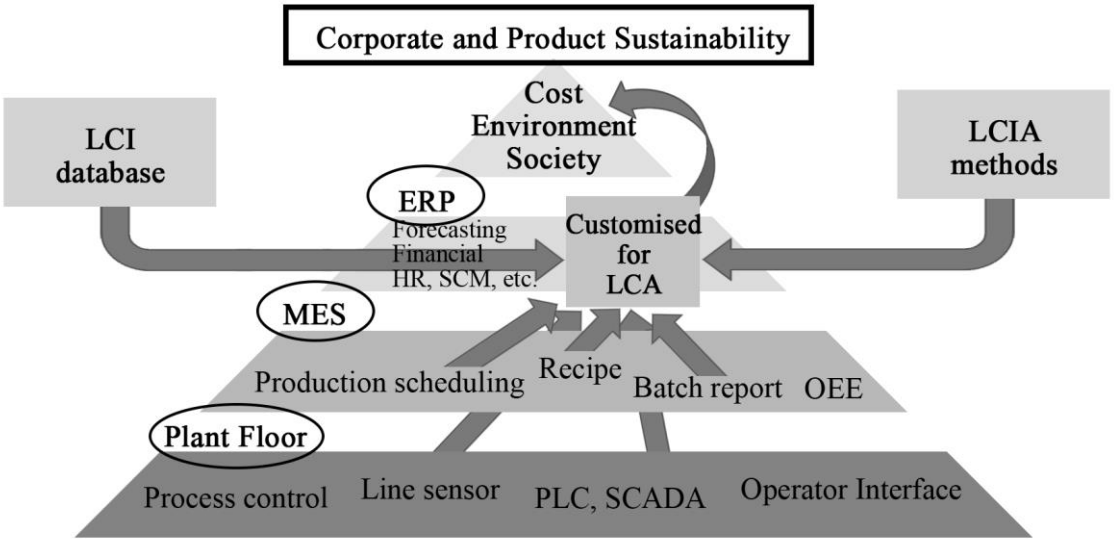

Figure 30: General framework for integrated product and organisational sustainability and data flux from the plant floor, the MES system, ERP systems, Life Cycle Inventory Databases, Impact Assessment Methods and their general translation toward corporate and product sustainability.

An exemplary data flux is given below to make the general framework represented in Figure 30 more tangible. As a simplification only the packaging phase of the product life cycle is taken into account. A packaging line in e.g. the life sciences industries consumes the following resources:

- Material resources: folding box, shipping box, plastics, euro pallet, wrapping foil, etc. These flows are generally available in the Bill of Materials, which can be extracted from procurement ERP applications.
- Energetic resources: power consumption of the packaging line, temperatures of heating air in case of sealing, flow rates of heating air, compressed air consumption, air pressure, HVAC, potentially nitrogen gas flow rates and pressures.

These flows are a lot more difficult to find and are scattered in the data management system. For some (e.g. flow rates) one might start from the flow rate sensor to the SCADA system which feeds information into the MES. Generally, one needs to extract these data from different data management systems.

- Auxiliary substances: cleaning media, C/O resources, maintenance resources, etc.

Once all flows with their flow properties (temperature, pressure) are extracted from different systems and sensors, mass and energy balances are generated in the customised LCA modules. These balances of the so-called foreground system need to be mapped with Life Cycle Databases, relating flows entering the site 'gate' to the cradle of resource consumption in order to generate a cumulative balance. Last, this so-called Life Cycle Inventory is subject to impact assessment calculations upon integration of Life Cycle Impact Assessment Methods (LCIAM) such as Carbon Footprinting and Resource Footprinting.

What has been elaborated in the previous paragraphs is exactly what is meant with multidisciplinarity. The multidisciplinary approach goes back to the very diverse team of professionals one needs to establish sustainability assessment modules for product stewardship, for sustainability reporting and for plant optimisation and integration of waste as resources. It is an approach where environmental engineers, business and SAP analysts, ICT experts and operational management professionals have to sit together to obtain the highest shared added value through one's supply chain and in-house operations. The next chapter provides a non-exclusive list of types of ERP modules for LCA and Life Cycle Sustainability Assessment (LCSA) in general.

9.3.2 The role of customised ERP modules for corporate and product sustainability assessments

As has been elaborated in the previous chapters customised ERP modules could offer solutions for automated sustainability assessments in manufacturing or SC environments where primary data tend to be measured but not or only partially penetrating through the MES layer. Depending on the availability, transparency and consistency of measured data (Chapter 9.2) from the production line and SC data of n-x suppliers, the role of the customised ERP module can differ substantially. The three subchapters below will highlight the use of regression analysis (touched upon in Chapter 9.2 as well), engineering modules and engineering design software such as ASPEN.

9.3.2.1 Coupling customised regression analysis with ERP systems for automated sustainability assessments

In environments where data are sufficiently being measured at the production line and process data penetration and transparency through the SC are satisfactory, regression analysis might offer a solution to generate LCA indicators such as CEENE (cumulative resource consumption) or Carbon Footprint directly from readily available data within ERP systems. The customised sustainability assessment module would result in a set of equations to automatically generate an environmental footprint (could be both resource driven and/or emission driven). This option could be classified as the most preferable solution when data measurements are relatively abundant, whether or not penetrating through the MES layer. Ideally through Machine Learning (ML), the module should be able to construct the set of equations and their coefficients (few of them have been proposed by De Soete et. al. (2014)) depending on the type of available data in order to reduce the uncertainty on the end result (Liu et al., 2007; De Soete et al., 2014b).

9.3.2.2 Coupling engineering modules with ERP systems for automated sustainability assessments

In Research and Development (R&D) or other data scarce environments where often prospective or enabling technologies are being tested, technology can be broken down into so-called unit operations (e.g. evaporation, crystallisation, absorption, etc.). Engineering models were developed in e.g. the European PROSUITE FP7 Project in order to build mass and energy balances of emerging technologies through a very modular approach based on basic unit operations (De Meester et al., 2011). These engineering models can be built in a modular way in ERP systems and linked with the input data of the engineering models. One should bear in mind that uncertainty and variability of the response variable will be characterized with a rather high uncertainty in coupling different unit operations, each of them having a certain degree of uncertainty. However, this pathway might be very promising for the future to anticipate on environmental burdens in an early R&D development stage (De Soete et al., 2014a).

9.3.2.3 Coupling process modelling software with ERP systems for automated sustainability assessments

A third example in this non-exhaustive list is the coupling of process engineering software such as ASPEN with business ERP systems. In this case the customised module serves as an interface between the modelling software and ERP and/or other enterprise resource systems. The modelling software is basically feeding into ERP systems in terms of integration of systems but maintains its stand-alone character. This can be a preferred option in design stages or if one wants to perform scenario analysis, etc. In terms of integration of process data and SC data it is probably the least preferred solution to foster shared value through the SC actors and automated corporate and product sustainability assessments through LCA and LCSA in general. Figure 31 exemplifies how a certain interface module could look like. The grey area resembles the software environment

while the green coloured boxes refer to the four basic steps of LCA. The system boundaries applied on the calculations in the modelling environments are indicated in yellow. Upon goal and scope definition of the LCA, system boundaries of the process (e.g. a chemical synthesis step) to be modelled are applied in ASPEN (optionally with supporting utilities such as solvent recuperation through distillation at the plant level, otherwise, these data are extracted from ERP systems or LCA databases). The inputs and outputs of the process are calculated and used to generate mass and energy balances which are then fed into the ERP module, where the Life Cycle Inventory (LCI, based on elementary flows only) is constructed through the connection of the mass and energy balances with the industrial metabolism through LCA databases. Upon multiplication with its characterisation factor, every environmental stressor of the LCI matrix is transformed into an environmental impact which is then – according to the method used – classified in midpoint or endpoint categories. The LCA results can be interpreted by the end-user through varies output options (report, tables, diagrams, etc.). This schedule is providing a plausible structure of combining data from different environments to ease the interpretation of the above proposed roles of ERP modules.

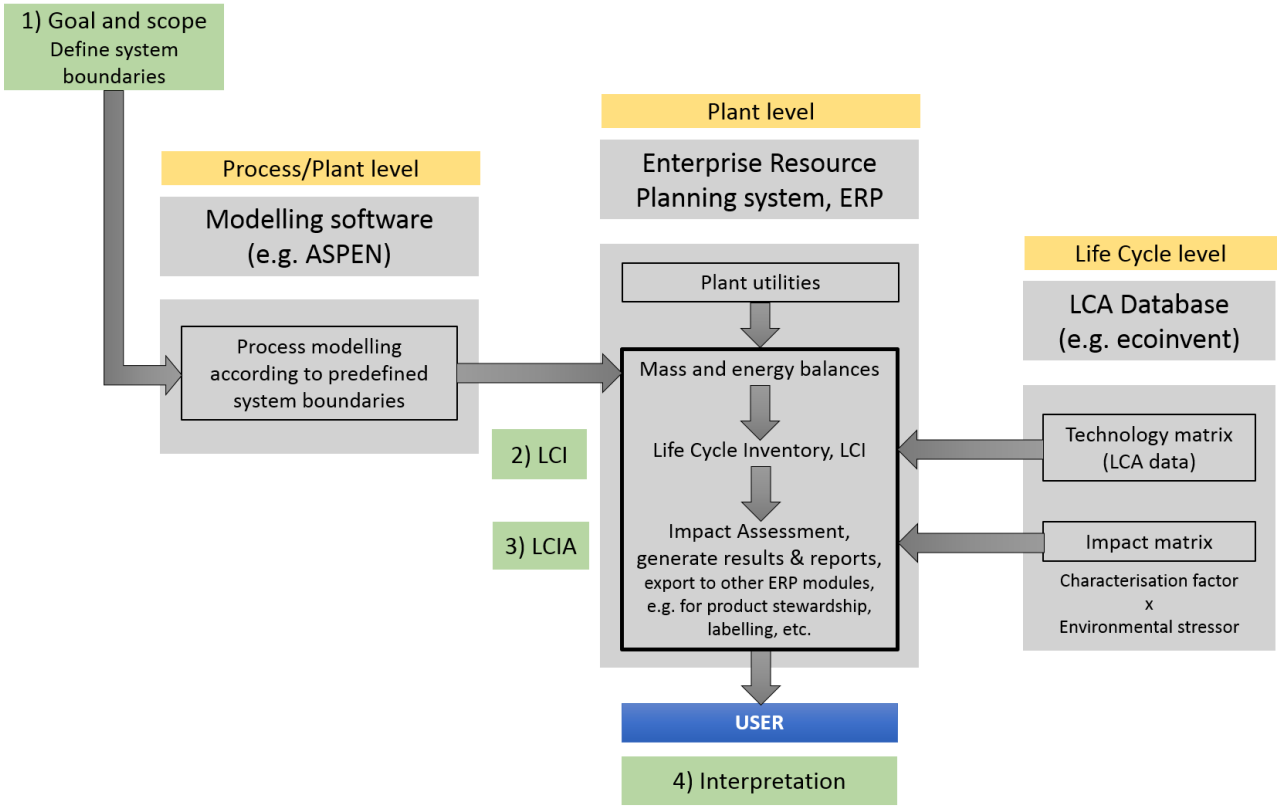

Figure 31: Schematic example of coupling process modelling software (e.g. ASPEN) with ERP systems through an interface module with LCA databases (e.g. ecoinvent). The grey area resembles the software environment while the green coloured boxes refer to the four basic steps of LCA. The system boundaries applied on the calculations in the modelling environments are indicated in yellow. This schedule is providing a plausible structure of combining data from different environments to ease the interpretation for the reader of the above proposed roles of ERP modules.

9.4 Conclusions and outlook

With this study, the author wanted to take the discussion in introducing environmental sustainability of products, services and enterprises into business Enterprise Resource Planning (ERP) systems one step further. These new ERP applications will foster the sustainability transparency and performance of organisations and their Supply Chains (SCs). Under the condition that appropriate business models protecting competitive advantages are applied, internal optimisation (continuous improvement) through the SC actors (n-1, n-2, n-x) can be achieved leading to shared value and Sustainable Supply Chain Management (SSCM), facilitated by e.g. the proposed customised ERP modules. To get to that point, six important potential bottlenecks were highlighted: (1) Data management in organisations; (2) Data penetration through Manufacturing Execution Systems (MES); (3) Consistency in data logging; (4) SC Transparency; (5) SC Reliability and (6) the language issue. This is a non-exhaustive list of challenges we are facing that should be further explored and investigated. One cannot highlight enough the importance in B2B communications through the SC to make that happen. SCs are complex systems that rarely rely on one sector, thus an inter-sectoral, multidisciplinary approach will be necessary. Not but the least important challenge most probably relies on the fact that building bridges between disciplines, between academics and industry is key in this age of science and information. More specifically, the field of Life Cycle Assessment (LCA) can adopt and apply a substantial amount of tools and lines of thought from operational management such as the Lean heritage and Six Sigma and vice versa; the Life Cycle Thinking (LCT) approach should be more embedded in continuous improvement actions and Operational Excellence in order to allocate resources in an efficient and effective way to real bottleneck operations. The next step to take would ideally be to validate this proposed framework by assembling a team with all

multidisciplinary aspects and evaluate to what extent and for wat use cases the different formats of a customised module would serve its needs.

Part 4: Overall Conclusions and Outlook

Chapter 10
Overall Conclusions and Outlook

10.1 Overall Conclusions of the Dissertation

To end this dissertation with, the author provides overall conclusions and connects the findings of the different chapters in a coherent end result of the work done during this PhD. Chapter 10.2 provides a concise guide towards further potential implementation of this the results PhD dissertation. Next, Chapter 10.3 until 10.5 disclose a research oriented outlook towards future perspectives in the field of (environmental sustainability assessment) in the pharmaceutical industry.

While Part 2 merely unveiled the resource footprint of Small (SM) and Large Molecules (LM), Part 3 focussed on the applications of Life Cycle Assessment (LCA) and process engineering related techniques within the pharmaceutical industry. Chapter 4 assessed what has been named in Green Chemistry principles (GC), process intensification and Lean manufacturing as 'introducing flow'. By introducing continuous manufacturing one does not only reduce lead times, enables pull production and creates value, one also reduces the resource footprint up to 34.0%. Continuous manufacturing has been postulated by many authors as one of the innovations of this decade in pharmaceutical manufacturing (Borukhova et al., 2015). The assessments done in this thesis were used in several business cases to put continuous manufacturing on the agenda as a more 'green' alternative next to the obvious cost saving aspect. Chapter 4 and Chapter 8 clearly revealed the very fossil intensive character of Small Molecule (SM) production through conventional chemical synthesis (up to 80% of the total resource footprint). It was of interest to investigate how this related to the environmental footprint of biologicals or so called LMs (Chapter 5). Against all expectations (a higher relative contribution of water and biotic renewables and a lower fossil resource contribution) the

fossil contribution to the resource footprint was only moderately lower in relative terms for the assessed LMs (in this case Monoclonal Antibodies, MABs) while the relative contribution of biotic renewable resources and land use was only moderately higher (on average 3.6 and 5.4% respectively). This is basically due to the fact that – even when the feedstock is biological (e.g. a cell culture) – industrial processing requires a high amount of fossil resources for fermentation and downstream processing (electricity for heating the bioreactor vessel jacket and for HVAC, etc.). Chapter 5 also touched upon the fact that a fair comparison on product level between SMs and LMs is hard to make (typically tablets for SMs and syringes for LMs). The LMs under study are long acting platforms for autoimmune diseases requiring only 6 parenteral administrations per year instead of one or two tablets a day (depending on the dose) for the SMs. On a compound base (product level) the cumulative resource consumption is about 4 times higher for the LMs compared to the SMs under analysis, while at treatment level (depending on the Defined Daily Dose of the WHO), the SMs score about 250 times worse than the LMs. These findings clearly reveal the need for system boundary expansion from the product level to the full pharmaceutical treatment level and eventually the healthcare pathway and thus a revision of the Functional Unit (FU) used for LCAs in the pharmaceutical and medical sector (De Soete et al., 2016b; Debaveye et al., 2016) (see Chapter 10.3 and 10.5).

Part 3 primarily consists out of a set of methodological advancements in the field of resource accounting, LCA and Life Cycle Thinking (LCT) to enhance the usability and value for business of implementing such techniques for assessing environmental sustainability. Chapter 6 starts with revealing the needs, bottlenecks and upcoming challenges for advancing the state of the art. This was done during an intensive study period performed at the European Commission's Joint Research Centre (JRC). Through

consulting more than 300 stakeholders in the field of environmental sustainability in the pharmaceutical and healthcare sector and by applying a set of methodologies (expert interviews, stakeholder surveys and roundtable discussions), the following priorities were set out as a strategic agenda for future research: (1) expand system boundaries to healthcare pathways instead of product level; (2) establish a 'Node' in the Life Cycle Data Network (LCDN) or a similar life cycle database to improve the availability of life cycle data on pharmaceutical production processes; (3) develop harmonised and standardised methods and (4) implement engineering software or LCA calculations into Enterprise Resource Planning (ERP) systems to enable process engineers to take into account environmental performance indicators. The next chapters tackle partially above mentioned challenges and provide potential answers to the questions postulated in the objective, Chapter 3. Chapter 7 showed that in upscaling technologies, from lab scale over pilot scale to full manufacturing scale, primarily resource consumption due to the use and production of utilities exponentially decreases. While in lab scale environments, electricity is often used for heating purposes (electrical heat exchangers), natural gas boilers are favoured in full manufacturing scale whenever possible. A predefined dose and recipe of cleaning media after a batch or campaign is usually applied at full manufacturing scale through Cleaning in Place (CIP), while in lab environments, cleaning is basically a manual operation through which a substantial amount of resources get lost. Chapter 8 illustrates the use of forecasting equations based on process variables as predictor variables in order to perform streamlined LCA. With only 1 to 5 readily available variables one can predict the cumulative resource consumption (or upon extension other impacts as well) of a chemical synthesis step with fairly well correlation coefficients (R^2) and Confidence Interval (CI) width. R^2 and CI width is mentioned for each of the models in Figure 28, Chapter 8.3.3 and Annex A6. This methodology has been adopted by the National Health Service of the UK to perform fast

calculations of the Carbon Footprint of their pharmaceuticals. This set of equations can be implemented in operational management tools (such as Enterprise Resource Planning, ERP systems) to calculate carbon or resource footprints with data measured from the production line. A framework of how this can be done and what could be the potential bottlenecks in e.g. data transparency and reliability through the Supply Chain (SC) is provided in Chapter 9. Below, an overall implementation guide of the methodologies developed during this work in operational management systems is given in Figure 24 and in Chapter 10.2.

10.2 An Implementation Guide of Methodologies Developed in This Work

As a number of methodologies were developed during this PhD research that can consequently lead towards implementation in industry, this section intends to provide a short guidance on how to perform this potential stepwise implementation. First, in order to introduce environmental performance indicators such as the resource footprint in R&D decision trees as criteria within certain stage gates, experience curves of technologies have to be derived (as was done in Chapter 7 for tabletting through wet granulation) (Step 1). The experience curve can be used to derive sustainability performance indicators for the development of other formulations through wet granulation by estimating the impact once the medicine has been launched on the market. For prospective technologies (not existing yet, so changing the compound and technology), engineering models can be developed based on basic operations that can be scaled up as such (PROSUITE, 2009).

Once the product is manufactured at full scale and environmental sustainability indicators are used in the design of it (Design for the Environment, DfE) (Step 1), one enters an environment that is typically very hard to quantify from an input-output point of view, typically not on a material base, but on utility base (electricity, natural gas, compressed air, cleaning media, different types of water, etc.). That is where forecasting calculations for streamlined LCA come into play. Based on few parameters, one can derive correlations equations (Step 2).

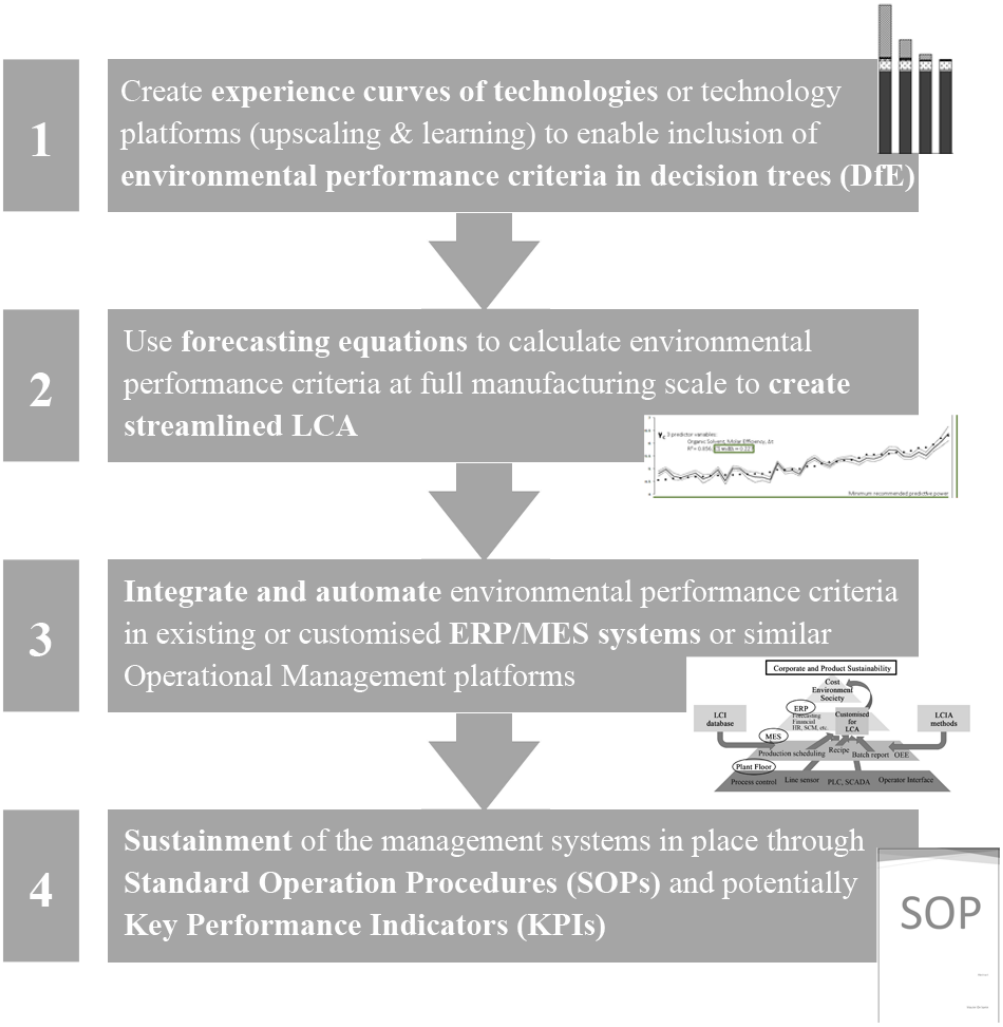

Figure 32: Implementation guide towards the integration of environmental sustainability assessments into operational management systems. Step 1 is the implementation of experience curves to include environmental performance criteria (Design for the Environment, DfE). Step 2 is the calculation of forecasting equations to enable streamlined LCA. Step 3 is the challenging implementation and integration of these equations in customised Enterprise Resource Planning (ERP) or alternatively Manufacturing Execution Systems (MES). The final step is the sustainment of change through the development of Standard Operation Procedures (SOPs) and potentially Key Performance Indicators (KPIs).

Once Step 2 is fulfilled for the desired processes or products, one has to integrate the calculations derived in Step 2 in operational management systems such as ERP systems (Step 3), which is a very challenging task. Various potential options are presented in this

dissertation in Chapter 9. Step 4 is probably the most challenging task, for which we go back to one of the most important principles of continuous improvement and Lean management: sustainment. Once change has been successfully implemented, it needs to be sustained or the efforts will be lost sooner than later. This is done through the development of Standard Operations Procedures (SOPs) in which all actions are described for operators (entering the correct information in ERP systems, etc.), for shift supervisors and process engineers up to the higher management. A well designed sustainment plan includes Key Performance Indicators (KPIs) to evaluate the performance of employees and equipment/systems. The construction of SOPs and well defined KPIs are out of scope of this dissertation and will be dependent on the manufacturing area. Nonetheless, sustainment is for sure key to accomplish change without losing the positive effects of the efforts made.

10.3 Methodological challenges through the Life Cycle

Next to the challenges that were identified by the sector in Chapter 6 through stakeholder consultations, the author takes the liberty of providing his overall outlook on methodological challenges for emerging future research to be conducted and challenges to be tackled. For sure, the full potential of economic and environmental cost savings has not been reached yet in the pharmaceutical sector. Step by step, authors are including more and more technological aspects and impact assessment concepts. Whereas 5 years ago scientists started to acknowledge we have to include the full production chain and not just the Active Pharmaceutical Ingredient (API), one is more and more reaching to a consensus that there is an emerging need for enlarging the system boundaries over

different business segments (many corporations have pharmaceutical products and consumer products). Environmental sustainability assessment is no longer an assessment of a bunch of chemicals and their production processes; one should enlarge system boundaries to complete healthcare pathways and eventually national and global healthcare systems. As a consequence, the life cycle community needs to rethink the concept of the Functional Unit (FU). In too many cases, the functionality or set of attributes the customer wants to pay for (equals value) is not reflected in the FU. An example from the medical sector: a patient is not paying for drugs. A patient is buying drugs but pays to get better, to become healthy again. Human health is exactly the value that the medical sector is delivering and this is in most cases not fully reflected in the FU (e.g. 1 kg of API, 1 tablet, etc.). Since this PhD thesis evolved in a chronological way from a very condensed view on the resource consumption of API production towards including more functionalities in the FU and thereby embracing more parts of the value chain, Table 12 provides a general overview of FUs applied through the different chapters and their rationale of choice.

Table 12: Overview of applied Functional Units through this thesis and their rationale of choice.

Chapter	Functional Unit	Rationale
CH4	Tablet of TRAMACET®	Focus on batch versus continuous tabletting within JNJ business plan. No implication of downstream processing
CH5	Finished packed Dosage Form Defined Daily Dose (DDD)	The rationale in CH5 is exactly to show the difference in shifting from a very compound based FU towards a more treatment based one
CH7	Daily intake of PREZISTA®	Comparison between two solid dose production platforms (2x400mg and 1x800mg)

CH8	Mole of API	High level approach of the absolute impact of APIs
	Mole of intermediate (IPI)	Increase amount of data points for backwards stepwise linear regression modelling and more detailed resolution

The work done is this PhD is mainly focused on the manufacturing Supply Chain (SC), which is indicated in red on Figure 33 and the red box in drug discovery and development (experience curves, Chapter 7). The wider Life Cycle (LC) include the upstream grey area and downstream use and End-of-Life phase in the green area (Pharmaceuticals in the Environment, PIE). The upper grey bar represents the timeline from drug discovery to the end of the accounted environmental impact in time. Between the first two crosses which is the drug discovery and development phase (including clinical trial phases), 10 000 molecules are to be screened and reduced to one API and a dosage form has to be developed. This period typically takes about 14 years (time to market). Next, if approved, manufacturing and marketing of the medicine takes place. Finally, there is the accumulated downstream environmental burden of 14 years of development and 6 years of manufacturing of which we unfortunately do not even know the time span.

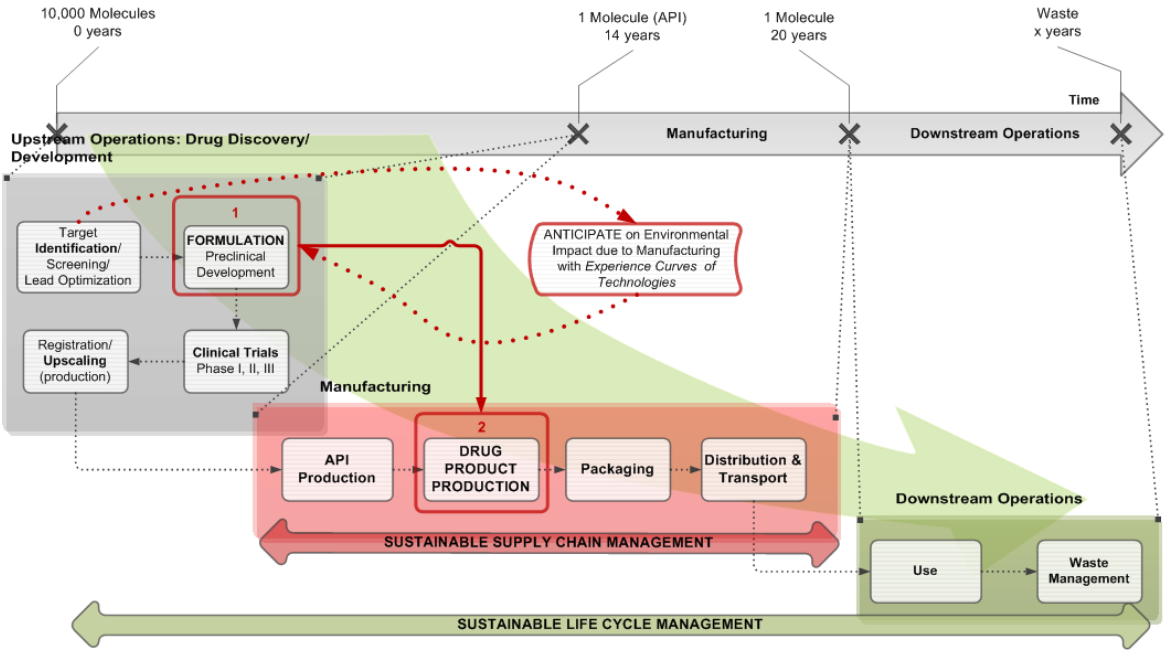

Figure 33: Sustainable Supply Chain Management (SSCM) versus Sustainable Life Cycle Management (SLCM). As was developed in Chapter 7, the figure includes an experience curve module on the Drug Product Production (DPP) manufacturing step in order to anticipate on the environmental impact in early R&D decision processes.

As soon as a potential lead molecule is found, a patent of typically 20 years is filed. Up to 14 years are spent on R&D, QA/QC, clinical trials, etc. A first generation medicine is in production for typically about 6 years (see Figure 33). Up to 40% of all revenue is (at least in Flanders) flowing back to R&D for new developments; a lot of - in terms of Lean manufacturing - Non Value Adding (NVA) processes are consuming resources (both capital and natural). In literature, no single LCA is to be found on the resources lost during the 14 years of testing, producing medicines for clinical trials, etc. It would be interesting to see what is the share of the burden of 14 years of R&D versus the manufacturing of a medicine, especially for low market volume products (e.g. STELARA®). The development of new, resource efficient platforms, new technologies should be evaluated. What is the impact and human benefit (functionality) of companion

diagnostics? Nanomedicines? Nano carriers as long acting platforms? Different types of medicinal products will require different approaches for a fair assessment. This modular, more generic approach is a huge challenge for the near future.

10.4 What is beyond the Micro Level?

An even broader societal research question is how global Value Chains (VCs) are affecting global supply mechanisms and competing with other human needs. Next to the process and company level, the macro level is pushing us more and more into research questions related to resource scarcity, supply disruption, global trade, etc. In order to calculate the dependency of the medical sector on scarce materials (e.g. critical raw materials in medical devices) and in order to analyse how the medical sector is embedded in the global industrial metabolism, a macro analysis should be made to see what is actually being delivered to the global medical sector and what comes out as a product. This, connected with market behaviour (which is far more complicated for pharmaceuticals than for consumer goods or retail products), import, export, etc. is to be investigated. To analyse how the medical sector is connected to e.g. chemistry and energy sectors, an Input-Output Assessment (IOA) is favourable. With that information we can put the impact at micro level of relatively 'low volume' products such as pharmaceuticals in perspective.

10.5 Coupling Operational Excellence and Life Cycle Assessment

During this PhD dissertation the author touched several times on the synergies between resource based LCA and the Lean heritage, being two very different approaches in the end striving for a similar goal: reduce resource consumption, increase efficiency and turn waste into resources. The truth is that both methodologies are very complementary in a way and can learn a lot from each other. Within LCA, an end to end approach, one can apply wide system boundaries, even wider after hybridisation with Input-Output Assessment (IOA) on a macro level. Unfortunately, when one adopts Lean instead of adapting it to the case, system boundaries are rather narrow potentially leading to shifting the bottleneck through the life cycle. An example: a process engineer from an end producer business asks for a Lean assessment on its production line because his Overall Equipment Efficiency (OEE) has dropped significantly the last few months (Work Station 4, WS4 on the Value Chain, VC presented in Figure 34). Through applying the Lean assessment toolbox, the OEE of the production line increased to a favourable extent because of a reduction in change over times (C/O), less speed loss and less unplanned downtime on WS4. After a few months, problems arise again because operational unit WS3 in the VC cannot keep up with the new lead time and unevenness is created leading to extra stock creation (yellow triangle in Figure 34) following upon the WS4, which is giving capacity issues in the warehouse following WS4 in the VC, etc. A story that is essentially leading to waste because of debottlenecking within too narrowly defined system boundaries.

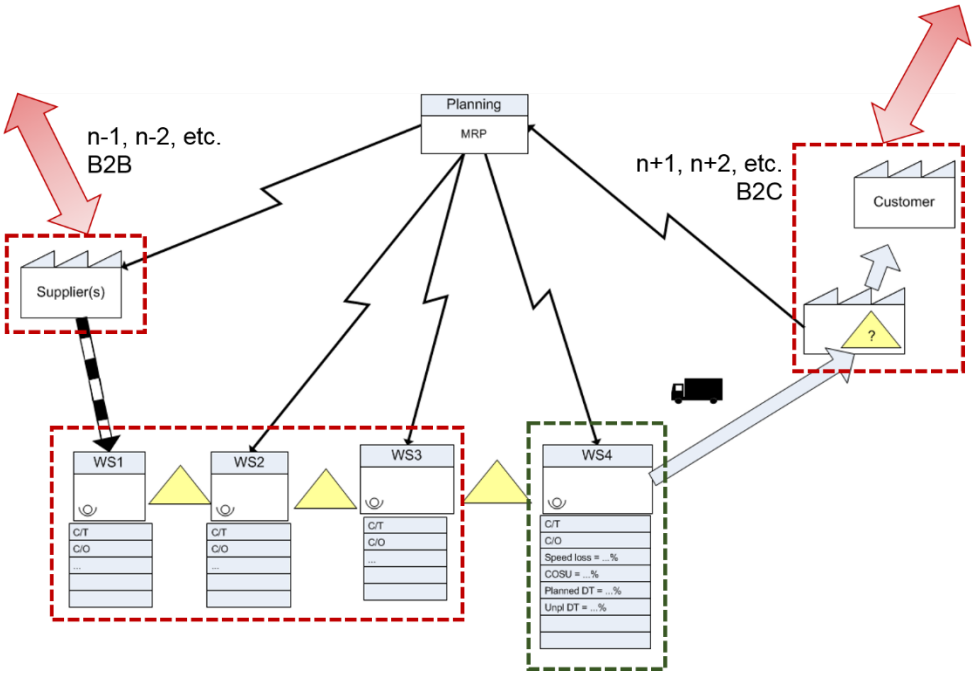

Figure 34: Value Chain (VC) representation of an end producer. A Lean assessment is performed on Work Station (WS) 4 (green dashed line) with operations having a red dashed line out of scope. After a few months, problems arise again because operational unit WS3 in the VC cannot keep up with the new lead time and unevenness is essentially leading to the creation of waste instead of value, due to debottlenecking within too narrowly defined system boundaries.

On the other hand, as Lean arouse from a business environment with one key priority: value, LCA can learn a lot from Value Assessments (VA) and Value Stream Mapping (VSM) to optimise the concept of the Functional Unit (FU) (as touched upon in Chapter 10.3). It would be very interesting to see a combined LCA/Lean assessment from a multidisciplinary point of view with as aim reducing environmental impacts for the highest value. The scope setting of an LCA could benefit from properly defining the characteristics a, b, c etc. of a certain product or service in its FU to really grasp the effort of making a qualitative product. Such a multidisciplinary approach is highly recommended to enhance the business relevance and valorisation potential of LCA results (De Soete et al., 2015). Figure 35 illustrates a possible framework to include VA in the scope setting of an LCA. This new area could convince more companies to

actually consider a combined LCA/Lean assessment from a multidisciplinary point of view with as aim reducing environmental impacts obtaining the highest value. More specifically, in addition to the commonly known framework of LCA (step one to four), the yellow arrows reflect initial Value Assessment (Engineering for Value) and as LCA is an iterative process (as are all sustainable improvement actions), Value Stream Managing (VSM) through the supply chain with – if needed – redesign. VA will help sustainability professionals and product/service designers to work together from the very beginning of the business model canvas. Through stakeholder consultation one should be able to identify to value attributes customers see in a certain product/service. If a physical attribute of a product is not valued by a group of customers (e.g. design of window frame with an insulation capacity that does not reach subsidy standards) or the other way around, a non-physical attribute such as the appreciation of the design of the window frame or colour, it will eventually change the value proposition of the product or service. Hence, customers only value what they are willing to pay for. From the Lean perspective, other attributes should be eliminated. From an integrated sustainability point of view, taking into account social aspects such as willingness to pay or consumer compliance, exactly the same holds. That is why – from a multidisciplinary point of view – LCA and Lean (more general Operational Excellence) should go hand in hand.

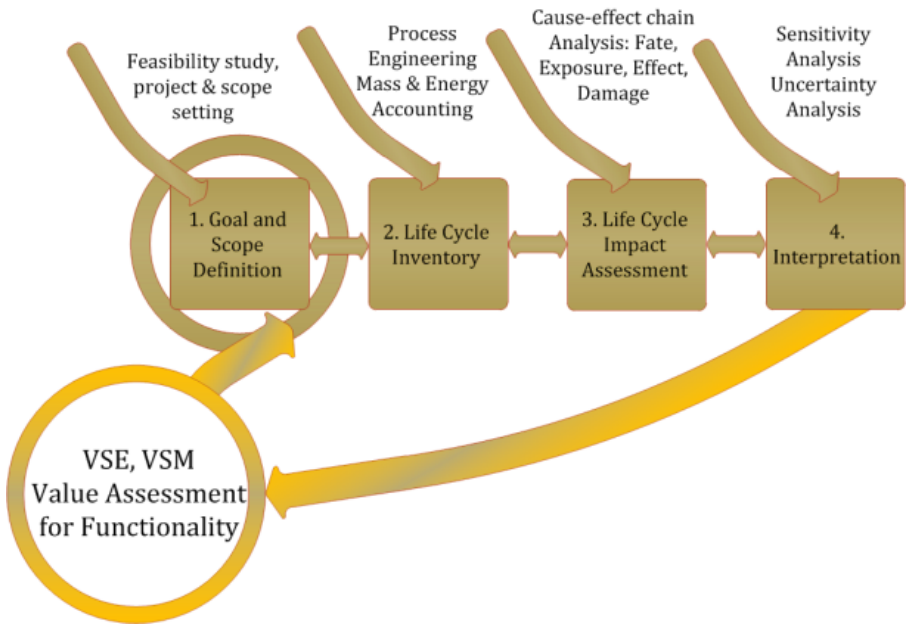

Figure 35: Conventional representation of the four basic steps of a Life Cycle Assessment (LCA) with addition of the concepts Value Stream Engineering (VSE) and Value Stream Management (VSM) for a fair accounting of value within functional properties of a commonly defined Functional Unit (FU) (De Soete et al., 2015).

The final paragraph of this dissertation embraces the author's personal advice from learnings experienced during this PhD work towards future research(ers). What they say is true: keep it simple. The very first page of this dissertation quotes Friedrich Wilhelm Nietzsche. Apply the quote to science and one will understand that the only way to analyse complex systems is to acknowledge its simplicity. Breaking down complex systems to sub and sub-subunit operations enables one to assess prospective technologies that are even not yet existing.

Curriculum Vitae

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OBJECTIVE

Most driven to analyse and optimise production processes from a lifecycle perspective with focus on operational performance and sustainability. With passion for Lean, Six Sigma and Business Administration, aiming at integrating LCA strategies in business management tools.

WORKING EXPERIENCE

January, 2016-present

RESEARCH DEVELOPMENT SUSTAINABILITY ASSESSMENT, Ghent University, EnVOC

- Research Development Sustainability Assessment Pharma & Raw Materials
- Research Coordination

- Project Coordinator Sustainability Support and Information Centre (SSIC) & BioFlex EIT Raw Materials (European Institute of Innovation and Technology)

June, 2015-October 2016

RESEARCHER SUSTAINABILITY PHARMA, European Commission, DG JRC, IES

- Short term project: Evaluation of EU Product Environmental Footprinting and Life Cycle Data Networks in the Pharmaceutical & Healthcare Sector

September, 2013-present

PHD RESEARCHER/TEACHING ASSISTANT, Ghent University, EnVOC

"*Enhancing the Business Value of Environmental Sustainability Assessments in the Pharmaceutical Industry*", cooperation with Janssen Pharmaceutica NV (Johnson & Johnson) and the European Commission (DG JRC)

- Assisting in research coordination and academic program coordination
- Social skills development within both an industrial and academic environment
- Advising LCA project strategy of Johnson & Johnson, support Corporate Product Stewardship Team, LCA Consultancy
- EC experience: Support in FP7 PROSUITE Project and Horizon 2020 MEASURE Project

July, 2012-August, 2013

PHD RESEARCHER, Ghent University, EnVOC

"*Development of an integrated generic screening tool for assessing sustainability of pharmaceutical production processes*", cooperation with Janssen Pharmaceutica NV (Johnson & Johnson)

- Supply Chain Analysis in Pharmaceutical Industry, LCA, sustainability analysis, resource efficiency
- Project planning, project management, coaching, publication of scientific papers, conference participation

2011-2012

MSc. Thesis: thermodynamic sustainability analysis of pharmaceutical production processes

"Exergy based Sustainability Assessment of Batch versus Continuous Wet Granulation based Tablet Manufacturing: a Cohesive Analysis at Three Different Levels"

Solvay Sustainable Chemistry Award 2011-2012 for best MSc. Thesis

Ghent University, Faculty of Bioscience Engineering, Environmental Organic Chemistry & Technology Research Group

Cooperation with Janssen Pharmaceutica NV, Janssen-Cilag SPA & *GEA* Pharma Systems NV – *Collette*™

- Modelling, thermodynamic process analysis, LCA, energy & resource consumption analysis

Working experience abroad at Janssen-Cilag SPA Latina, Italy (Engineering, EHS & Safety, Operations & Logistics, Validation)

EDUCATION

PHD IN BIOSCIENCE ENGINEERING 2012-2016

2014-2015

Postgraduate BLACK BELT IN LEAN MANUFACTURING AND SIX SIGMA

Ghent University, Faculty of Civil Engineering

2010-2012

MASTER OF BIOSCIENCE ENGINEERING, ENVIRONMENTAL TECHNOLOGY

Environmental Coordinator Type A

Solvay Sustainable Chemistry Award 2011-2012 for best MSc. Thesis

Ghent University, Faculty of Bioscience Engineering

Bachelor of Bioscience Engineering, Environmental Technology 2007-2011

Secondary Education:	**ASO Sciences-Mathematics**	2005-2007
	ASO Latin-Mathematics	2001-2005
	Sint-Lodewijkscollege Bruges	

HONOURS AND AWARDS

- **Laureate Solvay Sustainable Chemistry Award 2011-2012** for the best MSc. Thesis in the Bioscience Masters of Chemistry and Bioprocess Technology and Environmental Technology. Judged on industrial relevance, applicability and economic finality.
- Nominated for **IE-net Royal Flemish Engineering price** for the best MSc. Thesis 2011-2012.
- Nominated for **best poster award at SETAC Europe 19th Case Study Symposium**, Rome, Italy, 2013
- Nominated for **Taminco Green Footsteps Awards 2014** (Belgium)**:** Development of Sustainable Processes

TRAINING

OpenLCA Software Training 2013

GreenDelta GmbH, Berlin, Germany

Postgraduate course in LCA & environmental system analysis 2013

Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Project Management 2014

UGent Doctoral Schools of Bioscience Engineering, Ghent, Belgium

Input-Output and Hybrid LCA 2015

2.0-consulting, European Commission Joint Research Centre, Institute for Environmental Sustainability, Ispra, Italy

INTERNATIONALLY PEER REVIEWED PUBLICATIONS (10)

- **De Soete, W.**; Dewulf, J.; Cappuyns, P.; Van der Vorst, G.; Heirman, B.; Aelterman, W.; Schoeters, K.; Van Langenhove, H., Exergetic Sustainability Assessment of Batch versus Continuous Wet Granulation based Pharmaceutical Tablet Manufacturing: a Cohesive Analysis at Three Different Levels. *Green Chemistry* **2013,** *15*, (11), 3039 - 3048.
- **De Soete, W.**; Boone, L.; Willemse, F.; De Meyer, E.; Heirman, B.; Van Langenhove, H.; Dewulf, J., Environmental resource footprinting of drug manufacturing: Effects of scale-up and tablet dosage. *Resources, Conservation and Recycling* **2014,** *91*, (0), 82-88.
- **De Soete, W.**; Debaveye, S.; De Meester, S.; Van Der Vorst, G.; Aelterman, W.; Heirman, B.; Cappuyns, P.; Dewulf, J., Environmental Sustainability Assessments of Pharmaceuticals: an emerging Need for Simplification in Life Cycle Assessments. *Environ Sci Technol* **2014**.
- Laner, D.; Rechberger H.; **De Soete W.**; De Meester S.; Astrup T. F., Resource recovery from residual household waste: An application of exergy flow analysis and exergetic life cycle assessment. *Waste Management* **2015**, 46, 653-667.
- Debaveye, S.; **De Soete, W.**; De Meester, S.; Vandijck, D.; Heirman, B.; Kavanagh, S.; Dewulf, J., Human health benefits and burdens of a pharmaceutical treatment: Discussion of a conceptual integrated approach. Environmental Research **2016**, 144, 19-31.
- Sturtewagen, L.; **De Soete, W.**; Dewulf, J.; Lachat, C.; Lauryssen, S.; Heirman, B.; Rossi, F.; Schaubroeck, T., Resource use profile and nutritional value assessment of a typical Belgian meal, catered or home cooked, with pork or Quorn (TM) as protein source. *Journal of Cleaner Production*. **2016**, 112, 196-204
- **De Soete, W.**, Towards a Multidisciplinary Approach on Creating Value: Sustainability through the Supply Chain and ERP Systems. *Systems* **2016,** *4* (1), 16.
- Sfez, S.; Dewulf, J.; **De Soete, W.**; Schaubroeck, T.; Kralisch, D.; Mathieux, F.; De Meester, S., Toward a framework for Resource Efficiency evaluation: Recommendations for Development & Innovation Projects. *Journal of Cleaner Production* **2016,** *Submitted*.

- **De Soete, W.**; Jiménez-González, C.; Dahlin, P.; Dewulf, J., Challenges and Recommendations for Environmental Sustainability Assessments of Pharmaceutical Products in the Healthcare Sector. *Green Chemistry* **2016,** *Submitted*.
- **De Soete, W.**; Rentería Gámiz, A.; De Graaf, J.; Enos, M.; Morrison, L.; Heirman, B.; Dahlin, P.; Dewulf, J. The Environmental Sustainability of Biotechnologically Produced Medicines: Lessons Learned and Optimisation. *Nature Biotechnology* **2016,** *Submitted*.

OTHER PUBLICATIONS

- Janssen Pharmaceutica NV (2013). Verslag aan de samenleving, ecologische duurzaamheid. Exergiegebaseerde duurzaamheidsanalyse, Solvay Sustainable Chemistry Award.
- Janssen Pharmaceutica NV (2014). Janssen Sustainability. Does Your Diet Contribute to a Healthier Society? Janssen, University of Ghent and SODEXO Receive Award for Diet and Resource Study. October 22nd, 2014.
- Janssen Pharmaceutica NV (2014). Janssen Sustainability. Predicting a medicine's sustainability: A Janssen-University of Ghent collaborative project. July 8th, 2015.
- Janssen Pharmaceutica NV (2014). Janssen Sustainability. Snelle duurzaamheidsanalyse verkleint ecologische voetafdruk. 11 juni 2015.
- Janssen, L. (2015). Hoe duurzaam is uw medicijn? Mondiaal Nieuws (MO*). 23 augustus 2015.
- Heyman, T., CEO Janssen Pharmaceutica NV (2015). Being Prepared to evolve and change. Standing still is not an option, we have to evolve constantly. Editorial.
- Janssen Pharmaceutica NV (2015). New Technique, Value Creation. How Sustainable is your medication?

CONFERENCES (18)

- De Soete, W., Dewulf, J., Cappuyns, P., Van der Vorst, G., Heirman, B., Aelterman, W., & Schoeters, K. (2012). Exergy based sustainability assessment of batch versus continuous pharmaceutical tablet production. *IE-Net Awards*, Antwerp, Belgium. **Poster**.

- De Soete, W., Dewulf, J., Cappuyns, P., Van der Vorst, G., Heirman, B., Aelterman, W., & Schoeters, K. (2013). Exergy-based sustainability assessment of batch versus continuous tabletting in pharmaceutical formulation. *2nd International symposium on Green Chemistry (ISGC-2): Renewable carbon and eco-efficient processes*, La Rochelle, France. **Oral Presentation**.
- De Soete, W.; Boone, L.; Willemse, F.; De Meyer, E.; Heirman, B.; Van Langenhove, H.; Dewulf, J. (2013). Environmental Resource Footprinting of Drug Manufacturing: Effects of Scale Up and Drug Administration, *SETAC Europe 19th Case Study Symposium*, Rome, Italy; Poster Award Nomination. **Poster & Oral Presentation**.
- De Soete, W.; Debaveye, S.; De Meester, S.; Van Der Vorst, G.; Aelterman, W.; Heirman, B.; Cappuyns, P.; Dewulf, J. (2014). Environmental sustainability assessment of pharmaceutical synthesis steps: hotspot analysis and resource consumption modelling, *3rd [avniR] Conference*, Lille, France. **Poster**.
- De Soete, W. (2014). Exergetic sustainability assessment of batch versus continuous manufacturing: lessons learned in primary and secondary pharmaceutical manufacturing. Process Intensification, from Batch to Continuous, *Koninklijke Vlaamse Ingenieursvereniging (KVIV)*, Antwerp, Belgium. **Oral Presentation**.
- De Soete, W. (2014). The use of Life Cycle Assessment as an early R&D decision tool: bottlenecks and potential solutions. *Taminco Green Footsteps Awards*, Antwerp, Belgium. **Poster**.
- De Soete, W.; Debaveye, S.; De Meester, S.; Van Der Vorst, G.; Aelterman, W.; Heirman, B.; Cappuyns, P.; Dewulf, J. (2014). Streamlining Life Cycle Assessments: an Emerging Need for Simplification, *SETAC Europe 20th Case Study Symposium*, Novi Sad, Serbia. **Oral Presentation**.
- De Soete, W., Dewulf, J. (2015). Sustainability in pharma manufacturing and the pharma supply chain. *Environmental Sustainability in the Pharmaceutical Industry, ISPE Belgium Environmental Sustainability Event*, Wavre, Belgium. **Oral Presentation**.
- De Soete, W., Dewulf, J. (2015). How LCM can contribute in delivering value to customers: the issue of functionality. *7th International Life Cycle Management Conference*, Bordeaux, France. **Poster and Workshop Presentation**.
- De Soete, W., Rentería Gámiz, A., De Graaf, J., Heirman, B., Dahlin, P., Dewulf, J., (2015). Exergetic sustainability assessment of the value chain of a biotechnologically

manufactured drug compound, *SETAC Europe 21th Case Study Symposium*, Nysiros, Greece. **Oral Presentation** (presented by Schaubroeck, T.).

- De Soete, W., Rentería Gámiz, A., Dewulf J., (2015). Environmental sustainability assessment of batch versus continuous manufacturing: lessons learned in primary and secondary pharmaceutical manufacturing. *7th International Conference of the International Society of Lyophilization and Freeze-Drying*, Barcelona, Spain. **Poster** (presented by Rentería Gámiz, A.).
- De Soete, W., Pennington, D., Dewulf, J., (2015). Towards Streamlining and Harmonisation. *Sustainable Development in the Healthcare and Pharmaceutical Sector, SDHP Seminar*, Ispra, Italy. **Chair, Oral Presentations.**
- De Soete, W., Dewulf, J., (2015). Environmental Sustainability and the Lean Heritage: the Case of Continuous Pharmaceutical Manufacturing. *Pharmaceutical Solid State Research Cluster (PSSRC) Annual Meeting*, Ghent, Belgium. **Oral Presentation.**
- Huysveld, S., De Soete, W., Sturtewagen, L., Lauryssen, S., Rossi. F., Heirman, B., Lachat, C., Dewulf, J, Schaubroeck, T., (2015). MCA of the resource use profile and nutritional value of a typical Belgian meal, catered vs. home cooked, pork vs. Quorn™ as protein source. *34th Universal EXPO Milano 2015*, Milan, Italy. **Poster**.
- De Soete, W., De Meester, S., Dewulf, J., (2015). Sustainability Support and Information Centre (SSIC). *3rd annual High Level Conference of the European Innovation Partnership (EIP) on Raw Materials,* Brussels, Belgium. **Poster**.
- De Soete, W., Dewulf, J., (2016). Networks of Infrastructure (NOI): Sustainability Support and Information Centre (SSIC). *EIT Raw Materials Information and Brokerage Event*, Berlin, Germany. **Oral Presentation.**
- De Soete, W., Dewulf, J., (2016). Sustainability Support and Information Centre (SSIC). *SETAC EUROPE 26th Annual Meeting*, Nantes, France. **Poster, Session Chair**.
- De Soete, W., (2017). *8th International Life Cycle Management Conference*, Luxembourg. **Advisory Board, Session Chair**.

MSC. THESIS COACHING (6)

- "*Environmental Sustainability Assessment of Pharmaceutical Tablet Manufacturing*", 2012-2013

  A co-operation between Ghent University and Janssen Pharmaceutica NV

- "*Environmental Sustainability Evaluation of Active Pharmaceutical Ingredient Synthesis Steps by Exergy Analysis*", 2012-2013
  A co-operation between Ghent University and Janssen Pharmaceutica NV
- "*Resource Use Profile and Nutritional Value Assessment of a Canteen Meal; a Case Study on Pork vs. Quorn*", 2013-2014
  A co-operation between Ghent University, Janssen Pharmaceutica NV & SODEXO
  Awarded with the **Vandemoortele Healthy Food Award 2014** for best Thesis
- "*Biotechnological Production of Primary Pharmaceutical Compounds: an Environmental Sustainability Assessment*", 2013-2014
  A co-operation between Ghent University, Janssen Pharmaceutica NV and Janssen Biologics
  An Erasmus Mundus Project – UNESCO – TU Delft – Ghent University – University of Prague
- "*Environmental Sustainability Assessment (EU PEF, CF, CEENE) of Pharmaceutical Cold Chain Distribution"*, 2014-2015
  A co-operation between Ghent University and Janssen Pharmaceutica NV
  An Erasmus Mundus Project – UNESCO – TU Delft – Ghent University – University of Prague
- "*Environmental Sustainability Assessment of Pharmaceutical Manufacturing of Tablets for the Treatment of Schizophrenia"*, 2015-2016
  A co-operation between Ghent University and Janssen Pharmaceutica NV
  An Erasmus Mundus Project – UNESCO – TU Delft – Ghent University – University of Prague

TEACHING EXPERIENCE

- Clean Technology and Life Cycle Assessment, Practical exercises, software training, case study guidance. 2013-2014, 2014-2015, 2015-2016. At least 12 contact hours.
- Chemical Analytical Methods (Organic), Lab exercises. 2014-2015. 18 contact hours
- Process Engineering, Theoretical & practical exercises. 2014-2015, 2015-2016. 72 contact hours

LANGUAGE SKILLS

	Reading	Speaking	Writing
Dutch (native)	******	******	******
English	******	*****	******
French	****	**	***
German	**	*	**

INFORMATICS SKILLS

MS Office (Excel, Word, PowerPoint, Visio)	******
OpenLCA, SimaPro, GaBi	******
S-PLUS, SPSS	*****
MATLAB	*****
MAPLE	****
Adobe Photoshop CS2	***
JAVA, VBA	**

Bibliography

1) Al-Mohizea, A. M., Ahmed, M. O., Al-jenoobi, F. I., Mahrous, G. M. and Abdel-Rahman, A. A. (2007). "Formulation and Evaluation of Dried Yeast Tablets Using Different Techniques." European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik **67**(1): 253-259.

2) Alfonsi, K., Colberg, J., Dunn, P. J., Fevig, T., Jennings, S., Johnson, T. A., Kleine, H. P., Knight, C., Nagy, M. A., Perry, D. A. and Stefaniak, M. (2008). "Green Chemistry Tools to Influence a Medicinal Chemistry and Research Chemistry Based Organisation." Green Chemistry **10**(1): 31-36.

3) Alfonsín, C., Hospido, A., Omil, F., Moreira, M. T. and Feijoo, G. (2014). "PPCPS in Wastewater – Update and Calculation of Characterization Factors for Their Inclusion in LCA Studies." Journal of Cleaner Production **83**: 245-255.

4) Allenby, B. R. (1999). First International Symposium on Environmentally Conscious Design and Inverse Manufacturing, Proceedings. Los Alamitos, Ieee Computer Soc.

5) Alvarenga, R. A. F., Dewulf, J., Van Langenhove, H. and Huijbregts, M. A. J. (2013). "Exergy-Based Accounting for Land as a Natural Resource in Life Cycle Assessment." International Journal of Life Cycle Assessment **18**(5): 939-947.

6) Alvarez, M. A. A., Bayle, M. S., Garcia, C. G., Martin, R. M., Soto, M. R. E. and Martinez, M. E. D. (2004). "Socioeconomic Status and Resource Consumption in Primary Care." Anales De Pediatria **61**(4): 292.

7) Amini, S., Remmerswaal, J., Castro, M. and Reuter, M. (2007). "Quantifying the Quality Loss and Resource Efficiency of Recycling by Means of Exergy Analysis." Journal of Cleaner Production **15**(10): 907-913.

8) Andreakos, E., Taylor, P. C. and Feldmann, M. (2002). "Monoclonal Antibodies in Immune and Inflammatory Diseases." Current Opinion in Biotechnology **13**(6): 615-620.

9) Anastas, P. (2008). "Fusing Green Chemistry and Green Engineering: Designbuild at the Molecular Level." Green Chemistry **10**(6): 607-607.

10) Anastas, P. T. (2003). "Green Engineering and Sustainability." Environmental Science & Technology **37**(23): 423.

11) Anastas, P. T. and Warner, J. C. (1998). Green Chemistry: Theory and Practice. New York, Oxford University Press.

12) Anastas, P. T. and Zimmerman, J. B. (2003). "Design through the 12 Principles of Green Engineering." Environmental Science & Technology **37**(5): 94-101.

13) Apaiah, R. K., Linnemann, A. R. and van der Kooi, H. J. (2006). "Exergy Analysis: A Tool to Study the Sustainability of Food Supply Chains." Food Research International **39**(1): 1-11.

14) Azapagic, A. (1999). "Life Cycle Assessment and Its Application to Process Selection, Design and Optimisation." Chemical Engineering Journal **73**: 1-21.

15) Bande, C. and Debecker, D. (2012). "Using Sustainability Principles to Guide Investment Decisions." Chimica Oggi-Chemistry Today **30**(6): 48-50.

16) Banimostafa, A., Papadokonstantakis, S. and Hungerbuehler, K. (2015). "Retrofit Design of a Pharmaceutical Batch Process Considering "Green Chemistry and Engineering" Principles." Aiche Journal **61**(10): 3423-3440.

17) Bianchi, M., Cavaliere, A., Chiaroni, D., Frattini, F. and Chiesa, V. (2011). "Organisational Modes for Open Innovation in the Bio-Pharmaceutical Industry: An Exploratory Analysis." Technovation **31**(1): 22-33.

18) Bicheno, J. and Holweg, M. (2009). The Lean Toolbox: The Essential Guide to Lean Transformation. Buckingham, UK, PICSIE Books.

19) Bilgen, S., Kaygusuz, K. and Sari, A. (2007). "Thermodynamic Aspects of Energy Systems and Sustainable Development." Energy Sources, Part A: Recovery, Utilization, and Environmental Effects **30**(4): 325-333.

20) Boholm, M. and Arvidsson, R. (2014). "Controversy over Antibacterial Silver: Implications for Environmental and Sustainability Assessments." Journal of Cleaner Production **68**: 135-143.

21) Borukhova, S., Hessel, V., Kleinebudde, P., Khinast, J. and Rantanen, J. (2015). Continuous Manufacturing of Pharmaceuticals.

22) Borukhova, S., Noël, T. and Hessel, V. (2016). "Hydrogen Chloride Gas in Solvent-Free Continuous Conversion of Alcohols to Chlorides in Microflow." Organic Process Research & Development **20**(2): 568-573.

23) Bösch, M. E., Hellweg, S., Huijbregts, M. A. J. and Frischknecht, R. (2006). "Applying Cumulative Exergy Demand (CExD) Indicators to the Ecoinvent Database." The International Journal of Life Cycle Assessment **12**(3): 181-190.

24) Briggs, D. (2003). "Environmental Pollution and the Global Burden of Disease." British Medical Bulletin **68**: 1-24.

25) Broxterman, Q. B., Hughes, D. L. and Pyrz, W. D. (2011). "Pharma and Suppliers Collaborating on Green Chemistry Launch of Pmi Tool." Chimica Oggi-Chemistry Today **29**(5): 58.

26) Brundtland, G. H. (1987). "Our Common Future - Call for Action." Environmental Conservation **14**(4): 291-294.

27) Brunet, R., Guillen-Gosalbez, G. and Jimenez, L. (2014). "Combined Simulation-Optimization Methodology to Reduce the Environmental Impact of Pharmaceutical Processes: Application to the Production of Penicillin V." Journal of Cleaner Production **76**: 55-63.

28) Caduff, M., Huijbregts, M. A. J., Althaus, H.-J. and Hendriks, A. J. (2010). "Power-Law Relationships for Estimating Mass, Fuel Consumption and Costs of Energy Conversion Equipments." Environmental Science & Technology **45**(2): 751-754.

29) Caduff, M., Huijbregts, M. A. J., Althaus, H.-J., Koehler, A. and Hellweg, S. (2012). "Wind Power Electricity: The Bigger the Turbine, the Greener the Electricity?" Environmental Science & Technology **46**(9): 4725-4733.

30) Campion, N., Thiel, C. L., DeBlois, J., Woods, N. C., Landis, A. E. and Bilec, M. M. (2012). "Life Cycle Assessment Perspectives on Delivering an Infant in the Us." Science of The Total Environment **425**: 191-198.

31) Carmen Carnero, M. (2015). "Assessment of Environmental Sustainability in Health Care Organizations." Sustainability **7**(7): 8270-8291.

32) Castro, M. d. F., Mateus, R. and Braganca, L. (2015a). "A Critical Analysis of Building Sustainability Assessment Methods for Healthcare Buildings." Environment Development and Sustainability **17**(6): 1381-1412.

33) Castro, M. d. F., Mateus, R., Serodio, F. and Braganca, L. (2015b). "Development of Benchmarks for Operating Costs and Resources Consumption to Be Used in Healthcare Building Sustainability Assessment Methods." Sustainability **7**(10): 13222-13248.

34) Cespi, D., Beach, E. S., Swarr, T. E., Passarini, F., Vassura, I., Dunn, P. J. and Anastas, P. T. (2015). "Life Cycle Inventory Improvement in the Pharmaceutical Sector: Assessment of the Sustainability Combining Pmi and LCA Tools." Green Chemistry **17**(6): 3390-3400.

35) Cheung, M. S., Kashyap, V. and Phillips, M. (2014). "Increasing Supply Chain Reliability Shifting Paradigms." Chimica Oggi-Chemistry Today **32**(5): 60-62.

36) Ciriminna, R. and Pagliaro, M. (2013). "Green Chemistry in the Fine Chemicals and Pharmaceutical Industries." Organic Process Research & Development **17**(12): 1479-1484.

37) Ciroth, A., Graf, I. and Srocka, M. (2013). The OpenLCA Format Converter – New Release May 2013. Berlin, GreenDelta GmbH**:** 26.

38) Ciroth, A. and Srocka, M. (2008). "How to Obtain a Precise and Representative Estimate for Parameters in LCA - a Case Study for the Functional Unit." International Journal of Life Cycle Assessment **13**(3): 265-277.

39) Connor, A., Lillywhite, R. and Cooke, M. W. (2010). "The Carbon Footprint of a Renal Service in the United Kingdom." Qjm-an International Journal of Medicine **103**(12): 965-975.

40) Connor, A., Lillywhite, R. and Cooke, M. W. (2011). "The Carbon Footprints of Home and in-Center Maintenance Hemodialysis in the United Kingdom." Hemodialysis International **15**(1): 39-51.

41) Constable, D. J. C., Curzons, A. D. and Cunningham, V. L. (2002). "Metrics to 'Green' Chemistry - Which Are the Best?" Green Chemistry **4**(6): 521-527.

42) Constable, D. J. C., Curzons, A. D., Freitas dos Santos, L. M., Geen, G. R., Kitteringham, J., Smith, P., Hannah, R. E., McGuire, M. A., Webb, R. L., Yu, M., Hayler, J. D. and Richardson, J. E. (2001). "Green Chemistry Measures for Process Research and Development." Green Chemistry **3**(1): 7-9.

43) Constable, D. J. C., Dunn, P. J., Hayler, J. D., Humphrey, G. R., Leazer, J. L., Linderman, R. J., Lorenz, K., Manley, J., Pearlman, B. A., Wells, A., Zaks, A. and Zhang, T. Y. (2007). "Key Green Chemistry Research Areas - a Perspective from Pharmaceutical Manufacturers." Green Chemistry **9**(5): 411-420.

44) Cornelissen, R. L. (1997). Thermodynamics and Sustainable Development: The Use of Exergy Analysis and the Reduction of Irreversibility. PhD. Twente, University of Twente. **PhD:** 170.

45) Cornelissen, R. L. and Hirs, G. G. (2002). "The Value of the Exergetic Life Cycle Assessment Besides the LCA." Energy Conversion and Management **43**: 1417-1424.

46) Crabtree, R. (2010). Driving Operational Excellence: Succesful Lean Six Sigma Secrets to Improve the Bottom Line, MetaOps Publishing, LCC.

47) Cue, B. W. and Zhang, J. (2009). "Green Process Chemistry in the Pharmaceutical Industry." Green Chemistry Letters and Reviews **2**(4): 193-211.

48) Curzons, A. D., Constable, D. C. and Cunningham, V. L. (1999). "Solvent Selection Guide: A Guide to the Integration of Environmental, Health and Safety Criteria into the Selection of Solvents." Clean Products and Processes **1**(2): 82-90.

49) Curzons, A. D., Constable, D. J. C., Mortimer, D. N. and Cunningham, V. L. (2001). "So You Think Your Process Is Green, How Do You Know?-Using Principles of Sustainability to Determine What Is Green-a Corporate Perspective." Green Chemistry **3**(1): 1-6.

50) Curzons, A. D., Jimenez-Gonzalez, C., Duncan, A. L., Constable, D. J. C. and Cunningham, V. L. (2007). "Fast Life Cycle Assessment of Synthetic Chemistry (Flasc) Tool." International Journal of Life Cycle Assessment **12**(4): 272-280.

51) Daskalaki, I., Hennessey, P., Hubler, R. and Long, S. S. (2007). "Resource Consumption in the Infection Control Management of Pertussis Exposure among Healthcare Workers in Pediatrics." Infection Control and Hospital Epidemiology **28**(4): 412-417.

52) De Meester, B., Dewulf, J., Janssens, A. and Van Langenhove, H. (2006). "An Improved Calculation of the Exergy of Natural Resources for Exergetic Life Cycle Assessment (ELCA)." Environmental Science & Technology **40**(21): 6844–6851.

53) De Meester, S., Dewulf, J., Roes, L. and Patel, M. K. (2011). Prospective Sustainability Assessment of Technologies: Development of Basic Engineering Modules for Prospective Estimations of the Material Flows and Energy Requirements. Available from http://www.prosuite.org.

54) De Soete, W. (2012). Exergy-Based Sustainability Assessment of Batch Versus Continuous Tabletting in Pharmaceutical Formulation. Masterthesis. Ghent, Ghent University**:** 164.

55) De Soete, W. (2016). "Towards a Multidisciplinary Approach on Creating Value: Sustainability through the Supply Chain and ERP Systems." Systems **4**(1): 16.

56) De Soete, W., Boone, L., Willemse, F., De Meyer, E., Heirman, B., Van Langenhove, H. and Dewulf, J. (2014a). "Environmental Resource Footprinting of Drug Manufacturing: Effects of Scale-up and Tablet Dosage." Resources Conservation and Recycling **91**: 82-88.

57) De Soete, W., De Meester, S., Heirman, B. and Dewulf, J. (2015). How LCM Can Contribute in Delivering Value to Customers: The Issue of Functionality. 7th International conference of Life Cycle Management, Bordeaux, France.

58) De Soete, W., Debaveye, S., De Meester, S., Van der Vorst, G., Aelterman, W., Heirman, B., Cappuyns, P. and Dewulf, J. (2014b). "Environmental Sustainability Assessments of Pharmaceuticals: An Emerging Need for Simplification in Life Cycle Assessments." Environmental Science & Technology **48**(20): 12247-12255.

59) De Soete, W., Dewulf, J., Cappuyns, P., Van der Vorst, G., Heirman, B., Aelterman, W., Schoeters, K. and Van Langenhove, H. (2013). "Exergetic Sustainability Assessment of Batch Versus Continuous Wet Granulation Based Pharmaceutical Tablet Manufacturing: A Cohesive Analysis at Three Different Levels." Green Chemistry **15**(11): 3039 - 3048.

60) De Soete, W., Jiménez-González, C., Dahlin, P. and Dewulf, J. (2016a). "Challenges and Recommendations for Environmental Sustainability Assessments of Pharmaceutical Products in the Healthcare Sector." Green Chemistry **submitted**.

61) De Soete, W., Rentería Gámiz, A., De Graaf, J., Heirman, B., Dahlin, P., Enos, M., Morrison, L. and Dewulf, J. (2016b). "Small Molecules Versus Biologicals: The Environmental Resource Footprint." Nature Biotechnology **to be submitted**.

62) Debaveye, S., De Soete, W., De Meester, S., Vandijck, D., Heirman, B., Kavanagh, S. and Dewulf, J. (2016). "Human Health Benefits and Burdens of a Pharmaceutical Treatment: Discussion of a Conceptual Integrated Approach." Environmental Research **144**: 19-31.

63) Delgado, A. V. (2008). Exergy Evolution of the Mineral Capital on Earth. PhD Thesis. Zaragoza, University of Zaragoza, Department of Mechanical Engineering**:** 461.

64) DeVito, S. C., Keenan, C. and Lazarus, D. (2015). "Can Pollutant Release and Transfer Registers (Prtrs) Be Used to Assess Implementation and Effectiveness of Green

Chemistry Practices? A Case Study Involving the Toxics Release Inventory (TRI) and Pharmaceutical Manufacturers." Green Chemistry **17**(5): 2679-2692.

65) Dewulf, J., Benini, L., Mancini, L., Sala, S., Blengini, G. A., Ardente, F., Recchioni, M., Maes, J., Pant, R. and Pennington, D. (2015). "Rethinking the Area of Protection "Natural Resources" in Life Cycle Assessment." Environmental Science & Technology **49**(9): 5310-5317.

66) Dewulf, J., Bösch, M. E., De Meester, B., Van der Vorst, G., Van Langenhove, H., Hellweg, S. and Huijbregts, M. A. J. (2007a). "Cumulative Exergy Extraction from the Natural Environment (CEENE): A Comprehensive Life Cycle Impact Assessment Method for Resource Accounting." Environmental Science & Technology **41**: 8477-8483.

67) Dewulf, J., Van der Vorst, G., Aelterman, W., De Witte, B., Vanbaelen, H. and Van Langenhove, H. (2007b). "Integral Resource Management by Exergy Analysis for the Selection of a Separation Process in the Pharmaceutical Industry." Green Chemistry **9**(7): 785.

68) Dewulf, J. and Van Langenhove, H. (2002). "Assessment of the Sustainability of Technology by Means of a Thermodynamically Based Life Cycle Analysis." Environmental Science & Technology **9**(4): 267-273.

69) Dewulf, J. and Van Langenhove, H. (2004). "Thermodynamic Optimization of the Life Cycle of Plastics by Exergy Analysis." International Journal of Energy Research **28**(11): 969-976.

70) Dewulf, J., Van Langenhove, H., Mulder, J., van den Berg, M. M. D., van der Kooi, H. J. and de Swaan Arons, J. (2000). "Illustrations Towards Quantifying the Sustainability of Technology." Green Chemistry **2**(3): 108-114.

71) Dewulf, J., Van Langenhove, H., Muys, B., Bruers, S., Bakshi, B. R., Grubb, G. F., Paulus, D. M. and Sciubba, E. (2008). "Exergy: Its Potential and Limitations in Environmental Science and Technology." Environmental Science & Technology **42**(7): 2221-2232.

72) Dewulf, J., Van Langenhove, H. and Van De Velde, B. (2005). "Exergy-Based Efficiency and Renewability Assessment of Biofuel Production." Environmental Science & Technology **39**(10): 3878-3882.

73) Dewulf, J., Van Langenhove, H. and Vandamme, E. J. (2010). "Resource Technology - a Challenge for Scientists and Engineers." Journal of Chemical Technology and Biotechnology **85**(10): 1299-1300.

74) Dincer, I. and Rosen, M. A. (2004). "Exergy as a Driver for Achieving Sustainability." International Journal of Green Energy **1**(1): 1-19.

75) Draper, N. R. and Smith, H. (1981). Applied Regression Analysis, Wiley.

76) Drielsma, J. A., Russell-Vaccari, A. J., Drnek, T., Brady, T., Weihed, P., Mistry, M. and Simbor, L. P. (2016). "Mineral Resources in Life Cycle Impact Assessment-Defining the Path Forward." International Journal of Life Cycle Assessment **21**(1): 85-105.

77) Dunn, P. J. (2013). "Pharmaceutical Green Chemistry Process Changes - How Long Does It Take to Obtain Regulatory Approval?" Green Chemistry **15**(11): 3099-3104.

78) Dunn, P. J., Galvin, S. and Hettenbach, K. (2004). "The Development of an Environmentally Benign Synthesis of Sildenafil Citrate (Viagra™) and Its Assessment by Green Chemistry Metrics." Green Chemistry **6**(1): 43-48.

79) EC Directorate General for Health and Consumers (DG SANCO) (2013). Evaluation of the Use and Impact of the European Community Health Indicators Echi by Member States**:** 189.

80) EFPIA (2015). The Pharmaceutical Industry in Figures, EFPIA**:** 27.

81) EIT Raw Materials (2015). Our Knowledge & Innovation Themes, European Institute for Innovation and Technology (EIT)**:** 2.

82) Elkington, J. (1998). "Partnerships from Cannibals with Forks: The Triple Bottom Line of 21st-Century Business." Environmental Quality Management **8**(1): 37-51.

83) Ellery, T. and Hansen, N. (2012). Pharmeceutical Lifecycle Management: Making the Most of Each and Every Brand. Hoboken, New Jersey, John Wiley & Sons.

84) European Commission - Joint Research Centre - Institute for Environment and Sustainability (2010). International Reference Life Cycle Data System (ILCD) Handbook - General Guide for Life Cycle Assessment - Detailed Guidance, European Union.

85) European Commission - Joint Research Centre - Institute for Environment and Sustainability (2012). International Reference Life Cycle Data System (ILCD) Data Network - Compliance Rules and Entry-Level Requirements. Luxembourg, European Commission - Joint Research Centre - Institute for Environment and Sustainability.

86) European Commission (2008). EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Manufacture of Sterile Medicinal Products. DG Enterprise and Industry. Brussels**:** 16.

87) European Commission (2011). A Resource-Efficient Europe – Flagship Initiative under the Europe 2020 Strategy. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. Brussels, European Commission.

88) European Commission (2013). Commission Recommendation of 9 April 2013 on the Use of Common Methods to Measure and Communicate the Life Cycle Environmental Performance of Products and Organisations Text with EEA Relevance **2013/179/EU:** 169.

89) European Commission (2015a). Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Region. Closing the loop - An EU action plan for the Circular Economy. Brussels, European Commission**:** 21.

90) European Commission (2015b). "Directive 2005/32/EC of the European Parliament and of the Council." Official Journal of the European Union.

91) European Parliament (19/11/2008). Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on Waste and Repealing Certain Directives (Text with EEA Relevance).

92) EUROSTAT (2016). "Total General Government Expenditure." Retrieved February, 14, 2016, from

http://ec.europa.eu/eurostat/tgm/graph.do?tab=graph&plugin=1&language=en&pcode=tec00023&toolbox=type.

93) Faertes, D. (2015). Reliability of Supply Chains and Business Continuity Management. 3rd International Conference on Information Technology and Quantitative Management, ITQM 2015. L. Gomes, Colcher, R., Wolcott, P., HerreraViedma, E. and Shi, Y. **55:** 1400-1409.

94) Federsel, H.-J. (2013). "En Route to Full Implementation: Driving the Green Chemistry Agenda in the Pharmaceutical Industry." Green Chemistry **15**(11): 3105-3115.

95) Finnveden, G., Arushanyan, Y. and Brandão, M. (2016). "Exergy as a Measure of Resource Use in Life Cycle Assessment and Other Sustainability Assessment Tools." Resources **5**(3): 23.

96) Finnveden, G., Hauschild, M. Z., Ekvall, T., Guinee, J., Heijungs, R., Hellweg, S., Koehler, A., Pennington, D. and Suh, S. (2009). "Recent Developments in Life Cycle Assessment." Journal of environmental management **91**(1): 1-21.

97) Fischer, U. and Hungerbuhler, K. (2000). "Application of Indicators for Assessing Environmental Aspects of Chemical Processes to Case Studies from Pharmaceutical Production." Chimia **54**(9): 494-500.

98) Fortunak, J., Confalone, P. N. and Grosso, J. A. (2007). "Strength and Honor through the Pharmaceutical Industry's Embrace of Green Chemistry?" Current Opinion in Drug Discovery & Development **10**(6): 651-653.

99) Fortunak, J. M. (2009). "Current and Future Impact of Green Chemistry on the Pharmaceutical Industry." Future Medicinal Chemistry **1**(4): 571-575.

100) Franch-Lage, F., Amigo, J. M., Skibsted, E., Maspoch, S. and Coello, J. (2011). "Fast Assessment of the Surface Distribution of API and Excipients in Tablets Using NIR-Hyperspectral Imaging." International journal of pharmaceutics **411**(1-2): 27-35.

101) Frischknecht, R. and Rebitzer, G. (2005). "The Ecoinvent Database System: A Comprehensive Web-Based LCA Database." Journal of Cleaner Production **13**(13-14): 1337-1343.

102) Gad, S. C. (2008). Pharmaceutical Manufacturing Handbook: Production and Processes. Hoboken, New Jersey, John Wiley & Sons.

103) Gagliardino, J. J., Aschner, P., Baik, S. H., Chan, J., Chantelot, J. M., Ilkova, H., Ramachandran, A. and Investigators, I. (2012). "Patients' Education, and Its Impact on Care Outcomes, Resource Consumption and Working Conditions: Data from the International Diabetes Management Practices Study (Idmps)." Diabetes & Metabolism **38**(2): 128-134.

104) Gallou, F., Isley, N. A., Ganic, A., Onken, U. and Parmentier, M. (2016). "Surfactant Technology Applied toward an Active Pharmaceutical Ingredient: More Than a Simple Green Chemistry Advance." Green Chemistry **18**(1): 14-19.

105) Garcia-Reyes, J. F., Gilbert-Lopez, B. and Molina-Diaz, A. (2009). "Flow-through Solid-Phase Spectroscopy: A Contribution to Green Analytical Chemistry." Spectroscopy Letters **42**(6-7): 383-393.

106) García-Serna, J., Pérez-Barrigón, L. and Cocero, M. J. (2007). "New Trends for Design Towards Sustainability in Chemical Engineering: Green Engineering." Chemical Engineering Journal **133**(1-3): 7-30.

107) Gatenby, P. A. C. (2011). "Modelling the Carbon Footprint of Reflux Control." International Journal of Surgery **9**(1): 72-74.

108) Girod, B., Wiek, A., Mieg, H. and Hulme, M. (2009). "The Evolution of the IPCC's Emissions Scenarios." Environmental Science & Policy **12**(2): 103-118.

109) Glavic, P. and Lukman, R. (2007). "Review of Sustainability Terms and Their Definitions." Journal of Cleaner Production **15**(18): 1875-1885.

110) Goldratt, E. M. (1997). Critical Chain. Great Barrington, US, The North River Press Publishing Corporation.

111) Goldratt, E. M. and Cox, J. (2014). The Goal: A Process of Ongoing Improvement. Great Barrington, US, The North River Press Publishing Corporation.

112) Gong, M. (2005). "Exergy Analysis of a Pulp and Paper Mill." International Journal of Energy Research **29**: 79-93.

113) Gonzalez-Cortes, R., Lopez-Herce-Cid, J., Garcia-Figueruelo, A., Tesorero-Carcedo, G., Botran-Prieto, M. and Carrillo-Alvarez, A. (2011). "Prolonged Stay in Pediatric Intensive Care Units: Mortality and Healthcare Resource Consumption." Medicina Intensiva **35**(7): 417-423.

114) Gordeeva, Y. M. (2016). "Recent Developments in Eu Environmental Policy and Legislation." Journal for European Environmental & Planning Law **13**(1): 120-129.

115) Grießhammer, R., Benoît, C., Flysjö, A., Manhart, A., Mazijn, B., Méthot, A.-L. and Weidema, B. (2005). Feasibility Study : Integration of Social Aspects into LCA**:** 1-14.

116) Gu, F., Hall, P. and Miles, N. J. (2016). "Performance Evaluation for Composites Based on Recycled Polypropylene Using Principal Component Analysis and Cluster Analysis." Journal of Cleaner Production **115**: 343-353.

117) Gupta, P. and Mahajan, A. (2015). "Green Chemistry Approaches as Sustainable Alternatives to Conventional Strategies in the Pharmaceutical Industry." RSC Advances **5**(34): 26686-26705.

118) Hammond, G. P. (2007). "Industrial Energy Analysis, Thermodynamics and Sustainability." Applied Energy **84**(7-8): 675-700.

119) Hanel, T. and Felden, C. (2011). Does It Fit Together? State-of-the-Art of Academic Research Regarding to Manufacturing Execution Systems and Business Intelligence. Mechanical, Industrial, and Manufacturing Engineering. M. Ma. Newark, Information Engineering Research Inst, USA: 410-413.

120) Hartman, R., Helmy, R., Al-Sayah, M. and Welch, C. J. (2011). "Analytical Method Volume Intensity (Amvi): A Green Chemistry Metric for HPLC Methodology in the Pharmaceutical Industry." Green Chemistry **13**(4): 934-939.

121) Haswell, S. J. and Watts, P. (2003). "Green Chemistry: Synthesis in Micro Reactors." Green Chemistry **5**(2): 240-249.

122) Hatoum, H. T., Kong, S. X., Kania, C. M., Wong, J. M. and Mendelson, W. B. (1998). "Insomnia, Health-Related Quality of Life and Healthcare Resource Consumption - a Study of Managed-Care Organisation Enrollees." Pharmacoeconomics **14**(6): 629-637.

123) Herms, S. (2011). Exergy Flows in Product Life Cycles. Master Thesis. Delft, TUDelft. **MSc:** 98.

124) Hocking, R. R. (1976). "The Analysis and Selection of Variables in Linear Regression." Biometrics **32**: 1-49.

125) Holmner, A., Ebi, K. L., Lazuardi, L. and Nilsson, M. (2014). "Carbon Footprint of Telemedicine Solutions - Unexplored Opportunity for Reducing Carbon Emissions in the Health Sector." Plos One **9**(9).

126) Horvath, I. T. and Anastas, P. T. (2007). "Innovations and Green Chemistry." Chemical Reviews **107**(6): 2169-2173.

127) Huijbregts, M. A. J., Hellweg, S., Frischknecht, R., Hendriks, H. W. M., Hungerbuehler, K. and Hendriks, A. J. (2010). "Cumulative Energy Demand as Predictor for the Environmental Burden of Commodity Production." Environmental Science & Technology **44**(6): 2189-2196.

128) Huijbregts, M. A. J., Rombouts, L. J. A., Hellweg, S., Frischknecht, R., Jan Hendriks, A., Van De Meent, D., Ragas, M. J., Reijnders, L. and Struijs, J. (2006). "Is Cumulative Fossil Energy Demand a Useful Indicator for the Environmental Performance of Products?" Environmental Science & Technology **40**(3): 640-648.

129) Igos, E., Benetto, E., Venditti, S., Kohler, C., Cornelissen, A., Moeller, R. and Biwer, A. (2012). "Is It Better to Remove Pharmaceuticals in Decentralized or Conventional Wastewater Treatment Plants? A Life Cycle Assessment Comparison." Science of The Total Environment **438**: 533-540.

130) ISA (2015). Egovernment in the European Union. Brussels: 61.

131) ISO (2006). ISO 14040 - Environmental Management — Life Cycle Assessment — Principles and Framework. Geneva, ISO: 20.

132) Janssen-Cilag S.p.A. (2011a). Personal Communication. Latina.

133) Janssen-Cilag S.p.A. (2011b). Personal Interview. Latina, 2011.

134) Janssen Biotech Inc. (2016). "Stelara: Unique Mechanism of Action." Retrieved August 1st, 2016, from https://www.stelarahcp.com/plaque-psoriasis/mechanism-of-action.

135) Janssen Pharmaceutica NV (2004). Tramacet® Tablets Leaflet, TRAMACET® tablets Leaflet: 3.

136) Janssen Pharmaceutica NV (2013). Personal Communication. Beerse, Belgium.

137) Jiménez-González, C. (2000). Life Cycle Assessment in Pharmaceutical Applications. Chemical Engineering. Raleigh, NC, North Carolina State University. **PhD:** 257.

138) Jiménez-González, C., Curzons, A. D., Constable, D. J. C. and Cunningham, V. L. (2004a). "Cradle-to-Gate Life Cycle Inventory and Assessment of Pharmaceutical Compounds." International Journal of Life Cycle Assessment **9**(2): 114-121.

139) Jiménez-González, C., Curzons, A. D., Constable, D. J. C. and Cunningham, V. L. (2004b). "Expanding Gsks Solvent Selection Guide - Application of Life Cycle Assessment to Enhance Solvent Selections." Clean Technologies and Environmental Policy **7**(1): 42-50.

140) Jiménez-González, C., Ollech, C., Pyrz, W., Hughes, D., Broxterman, Q. B. and Bhathela, N. (2013). "Expanding the Boundaries: Developing a Streamlined Tool for Eco-Footprinting of Pharmaceuticals." Organic Process Research & Development **17**(2): 239-246.

141) Jimenez-Gonzalez, C. and Overcash, M. R. (2014). "The Evolution of Life Cycle Assessment in Pharmaceutical and Chemical Applications - a Perspective." Green Chemistry **16**(7): 3392-3400.

142) Jiménez-González, C., Poechlauer, P., Broxterman, Q. B., Yang, B.-S., am Ende, D., Baird, J., Bertsch, C., Hannah, R. E., Dell'Orco, P., Noorman, H., Yee, S., Reintjens, R., Wells, A., Massonneau, V. and Manley, J. (2011). "Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers." Organic Process Research & Development **15**(4): 900-911.

143) Jimenez-Gonzalez, C., Ponder, C. S., Broxterman, Q. B. and Manley, J. B. (2011). "Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry to Drive More Sustainable Processes." Organic Process Research & Development **15**(4): 912-917.

144) Jiménez-González, C. and Woodley, J. M. (2010). "Bioprocesses: Modelling Needs for Process Evaluation and Sustainability Assessment." Computers & Chemical Engineering **34**(7): 1009-1017.

145) Joshi, U. J., Gokhale, K. M. and Kanitkar, A. P. (2011). "Green Chemistry: Need of the Hour." Indian Journal of Pharmaceutical Education and Research **45**(2): 168-174.

146) Kainuma, Y. and Tawara, N. (2006). "A Multiple Attribute Utility Theory Approach to Lean and Green Supply Chain Management." International Journal of Production Economics **101**(1): 99-108.

147) Kaur, P., Sharma, H., Rana, R., Prasad, D. N. and Singh, R. K. (2012). "Comparative Study of Various Green Chemistry Approaches for the Efficient Synthesis of 1,4-Dihydropyridines." Asian Journal of Chemistry **24**(12): 5649-5651.

148) Kavvada, A., Ruiz-Barradas, A. and Nigam, S. (2013). "Amo's Structure and Climate Footprint in Observations and IPCC AR5 Climate Simulations." Climate Dynamics **41**(5-6): 1345-1364.

149) Khetan, S. K. and Collins, T. J. (2007). "Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry." Chemical Reviews **107**(6): 2319-2364.

150) Kim, S., Jiménez-González, C. and Dale, B. E. (2009). "Enzymes for Pharmaceutical Applications—a Cradle-to-Gate Life Cycle Assessment." The International Journal of Life Cycle Assessment **14**(5): 392-400.

151) Koel, M. and Kaljurand, M. (2006). "Application of the Principles of Green Chemistry in Analytical Chemistry." Pure and Applied Chemistry **78**(11): 1993-2002.

152) Koroneos, C., Spachos, T. and Moussiopoulos, N. (2003). "Exergy Analysis of Renewable Energy Sources." Renewable Energy **28**(2): 295-310.

153) Kralisch, D., Minkov, N., Manent, A., Rother, E., Mohr, L., Schowanek, D., Sfez, S., Lapkin, A., Jones, M., Meester, S. D., Soete, W. D., Dewulf, J., Bach, V., Finkbeiner, M., Weyell, P., Yaseneva, P., Jeswani, H., Azapagic, A. and Vanhoof, G. (2016). Roadmap for Sustainability Assessment in European Process Industries**:** 61.

154) Kralisch, D., Ott, D. and Gericke, D. (2015). "Rules and Benefits of Life Cycle Assessment in Green Chemical Process and Synthesis Design: A Tutorial Review." Green Chemistry **17**(1): 123-145.

155) Kuemmerer, K. (2007). "Sustainable from the Very Beginning: Rational Design of Molecules by Life Cycle Engineering as an Important Approach for Green Pharmacy and Green Chemistry." Green Chemistry **9**(8): 899-907.

156) Kümmerer, K. (2008). Pharmaceuticals in the Environment, Springer Berlin Heidelberg.

157) Lapkin, A. and Constable, D. J. C. (2009). Green Chemistry Metrics: Measuring and Monitoring Sustainable Processes. Chichester, West Sussex, John Wiley and Sons.

158) Leahy, D. K., Tucker, J. L., Mergelsberg, I., Dunn, P. J., Kopach, M. E. and Purohit, V. C. (2013). "Seven Important Elements for an Effective Green Chemistry Program: An IQ Consortium Perspective." Organic Process Research & Development **17**(9): 1099-1109.

159) Leekha, S., Thompson, R. L. and Sampathkumar, P. (2009). "Epidemiology and Control of Pertussis Outbreaks in a Tertiary Care Center and the Resource Consumption Associated with These Outbreaks." Infection Control and Hospital Epidemiology **30**(5): 467-473.

160) Lenzen, M., Wood, R. and Wiedmann, T. (2010). "Uncertainty Analysis for Multi-Region Input-Output Models - a Case Study of the UK's Carbon Footprint." Economic Systems Research **22**(1): 43-63.

161) Ley, S. V. (2012). "On Being Green: Can Flow Chemistry Help?" Chemical Record **12**(4): 378-390.

162) Li, X. J., Wang, P. and Huang, X. (2012). The Model of Equipment Integrated Maintenance Management Based on Mes. Mechatronics and Information Technology, Pts 1 and 2. Q. Han, Takahashi, K., Oh, C. H. and Luo, Z. Stafa-Zurich, Trans Tech Publications Ltd. **2-3:** 749-754.

163) Li, Z., Sobek, A. and Radke, M. (2016). "Fate of Pharmaceuticals and Their Transformation Products in Four Small European Rivers Receiving Treated Wastewater." Environmental Science & Technology **50**(11): 5614-5621.

164) Liker, J. K. and Convis, G. L. (2012). The Toyota Way to Lean Leadership: Achieving and Sustaining Excellence through Leadership Development. US, The McGraw-Hill Companies.

165) Lim, A. E. K., Perkins, A. and Agar, J. W. M. (2013). "The Carbon Footprint of an Australian Satellite Haemodialysis Unit." Australian Health Review **37**(3): 369-374.

166) Liu, Y. B., Wang, J. M., Sun, J. G. and Acm (2007). A Machine Learning Approach to Semi-Automating Workflow Staff Assignment. New York, Assoc Computing Machinery.

167) M'Hamed, M. O. (2015). "Ball Milling for Heterocyclic Compounds Synthesis in Green Chemistry: A Review." Synthetic Communications **45**(22): 2511-2528.

168) Malthus, T. R. (1798). An Essay on the Principle of Population. London, UK, J. Johnson, in St. Paul's Church-yard.

169) Manca, A., Kumar, K., Taylor, R. S., Jacques, L., Eldabe, S., Meglio, M., Molet, J., Thomson, S., O'Callaghan, J., Eisenberg, E., Milbouw, G., Buchser, E., Fortini, G., Richardson, J., Taylor, R. J., Goeree, R. and Sculpher, M. J. (2008). "Quality of Life, Resource Consumption and Costs of Spinal Cord Stimulation Versus Conventional Medical Management in Neuropathic Pain Patients with Failed Back Surgery Syndrome (Process Trial)." European Journal of Pain **12**(8): 1047-1058.

170) Marsh, K., Ganz, M. L., Hsu, J., Strandberg-Larsen, M., Gonzalez, R. P. and Lund, N. (2016). "Expanding Health Technology Assessments to Include Effects on the Environment." Value in Health.

171) Martin, A., Batty, A., Roberts, J. A. and Standaert, B. (2009). "Cost-Effectiveness of Infant Vaccination with Rix4414 (Rotarix™) in the UK." Vaccine **27**(33): 4520-4528.

172) Martinez, M., Augsburger, L., Johnston, T. and Jones, W. W. (2002). "Applying the Biopharmaceutics Classification System to Veterinary Pharmaceutical Products Part I: Biopharmaceutics and Formulation Considerations." Advanced drug delivery reviews **54**(6): 805-824.

173) Martyn, D., Kocharian, R., Lim, S., Meckley, L. M., Miyasato, G., Prifti, K., Rao, Y., Riebman, J. B., Scaife, J. G., Soneji, Y. and Corral, M. (2015). "Reduction in Hospital Costs and Resource Consumption Associated with the Use of Advanced Topical Hemostats During Inpatient Procedures." Journal of Medical Economics **18**(6): 474-481.

174) Mastrandrea, M. D., Mach, K. J., Plattner, G. K., Edenhofer, O., Stocker, T. F., Field, C. B., Ebi, K. L. and Matschoss, P. R. (2011). "The IPCC AR5 Guidance Note on Consistent

Treatment of Uncertainties: A Common Approach across the Working Groups." Climatic Change **108**(4): 675-691.

175) McDonough, W., Braungart, M., Anastas, P. T. and Zimmerman, J. B. (2003). "Applying the Principles of Green Engineering to Cradle-to-Cradle Design." Environmental Science & Technology **37**(23): 434-441.

176) McGonagle, F. I., Sneddon, H. F., Jamieson, C. and Watson, A. J. B. (2014). "Molar Efficiency: A Useful Metric to Gauge Relative Reaction Efficiency in Discovery Medicinal Chemistry." ACS Sustainable Chemistry & Engineering **2**(3): 523-532.

177) Meadows, D. H. and Meadows, D. (2007). "The History and Conclusions of the Limits to Growth." System Dynamics Review **23**(2-3): 191-197.

178) Mol, A. P. J. (2015). "Transparency and Value Chain Sustainability." Journal of Cleaner Production **107**: 154-161.

179) Molina-Diaz, A., Garcia-Reyes, J. F. and Gilbert-Lopez, B. (2010). "Solid-Phase Spectroscopy from the Point of View of Green Analytical Chemistry." Trac-Trends in Analytical Chemistry **29**(7): 654-666.

180) Morris, D. R. and Szargut, J. (1986). "Standard Chemical Exergy of Some Elements and Compounds on the Planet Earth." Energy **11**(8): 733-755.

181) Mosteller, F. and Tukey, J. W. (1977). Data Analysis and Regression, Addison-Wesley.

182) NHS Sustainable Development Unit (2012). Goods and Services Carbon Hotspots. Cambridge, NHS**:** 39.

183) Nisiwaki, M. (2003). "Green Chemistry in Process Research and Development in Pharmaceutical Industry." Journal of Synthetic Organic Chemistry Japan **61**(5): 464-471.

184) OECD/EU (2014). Health at a Glance: Europe 2014, OECD Publishing Paris.

185) Optenberg, S. A., Lanctot, K. L., Herrmann, N. and Oh, P. I. (2002). "Antidepressant Selection, Healthcare Resource Consumption and Costs in a Large Workplace Environment - US and Canadian Perspectives." Clinical Drug Investigation **22**(10): 685-694.

186) Osorio, A. C. P., da Cunha, A. L. M. C., Khan, S., Franco, C. J., Pereira-Netto, A. D. and Aucelio, R. Q. (2014). "Photochemical Derivatization of Amitriptyline Using a Green Chemistry Approach: Fluorimetric Determination and Photochemical Reaction Mechanism." Analytical Methods **6**(12): 4022-4028.

187) Ott, D., Borukhova, S. and Hessel, V. (2016). "Life Cycle Assessment of Multi-Step Rufinamide Synthesis - from Isolated Reactions in Batch to Continuous Microreactor Networks." Green Chemistry **18**(4): 1096-1116.

188) Ott, D., Kralisch, D., Dencic, I., Hessel, V., Laribi, Y., Perrichon, P. D., Berguerand, C., Kiwi-Minsker, L. and Loeb, P. (2014). "Life Cycle Analysis within Pharmaceutical Process

Optimization and Intensification: Case Study of Active Pharmaceutical Ingredient Production." ChemSusChem **7**(12): 3521-3533.

189) Passer, A., Lasvaux, S., Allacker, K., De Lathauwer, D., Spirinckx, C., Wittstock, B., Kellenberger, D., Gschoesser, F., Wall, J. and Wallbaum, H. (2015). "Environmental Product Declarations Entering the Building Sector: Critical Reflections Based on 5 to 10 Years Experience in Different European Countries." International Journal of Life Cycle Assessment **20**(9): 1199-1212.

190) Penny, T., Collins, M., Whiting, A. and Aumônier, S. (2015). Care Pathways: Guidance on Appraising Sustainability. London, COALITION FOR SUSTAINABLE PHARMACEUTICALS AND MEDICAL DEVICES**:** 51.

191) Perez-Lopez, P., Gonzalez-Garcia, S., Ulloa, R. G., Sineiro, J., Feijoo, G. and Teresa Moreira, M. (2014). "Life Cycle Assessment of the Production of Bioactive Compounds from Tetraselmis Suecica at Pilot Scale." Journal of Cleaner Production **64**: 323-331.

192) Polatli, M., Ben Kheder, A., Wali, S., Javed, A., Khattab, A., Mahboub, B., Iraqi, G., Nejjari, C., Tarıght, S., Koniski, M.-L., Rashid, N., El Hasnaoui, A. and Grp, B. S. (2012). "Chronic Obstructive Pulmonary Disease and Associated Healthcare Resource Consumption in the Middle East and North Africa: The Breathe Study." Respiratory Medicine **106**: S75-S85.

193) Pollard, A. S., Paddle, J. J., Taylor, T. J. and Tillyard, A. (2014). "The Carbon Footprint of Acute Care: How Energy Intensive Is Critical Care?" Public Health **128**(9): 771-776.

194) PROSUITE (2009). "Development and Application of a Stardardized Methodology for the Prospective Sustainability Assessment of Technologies (Prosuite)." 2.

195) Ramasamy, S. V., Titchener-Hooker, N. J. and Lettieri, P. (2015). "Life Cycle Assessment as a Tool to Support Decision Making in the Biopharmaceutical Industry: Considerations and Challenges." Food and Bioproducts Processing **94**: 297-305.

196) Rastogi, T., Leder, C. and Kuemmerer, K. (2014). "Designing Green Derivatives of Beta-Blocker Metoprolol: A Tiered Approach for Green and Sustainable Pharmacy and Chemistry." Chemosphere **111**: 493-499.

197) Recchioni, M., Blengini, G. A., Fazio, S., Mathieux, F. and Pennington, D. (2015). "Challenges and Opportunities for Web-Shared Publication of Quality-Assured Life Cycle Data: The Contributions of the Life Cycle Data Network." The International Journal of Life Cycle Assessment **20**(7): 895-902.

198) Rees, H. (2011). Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticals and Biologics. Singapore, John Wiley & Sons.

199) Res, M. D., Bresfelean, V. P., Ghisoiu, N. and Popa, S. C. (2011). "Research on the Implementation of Customized ERP Solutions for Improving Business Organization." Proceedings of the 6th International Conference on Business Excellence, Vol 2: 144-147.

200) Roggeri, D. P., Roggeri, A., Rossi, E., Cinconze, E., De Rosa, M., Maggioni, A. P. and Observ, A. C. (2014). "Direct Healthcare Costs and Resource Consumption after Acute

Coronary Syndrome: A Real-Life Analysis of an Italian Subpopulation." European Journal of Preventive Cardiology **21**(9): 1090-1096.

201) Roschangar, F., Sheldon, R. A. and Senanayake, C. H. (2015). "Overcoming Barriers to Green Chemistry in the Pharmaceutical Industry - the Green Aspiration Level™ Concept." Green Chemistry **17**(2): 752-768.

202) Russell, A., Ekvall, T. and Baumann, H. (2005). "Life Cycle Assessment – Introduction and Overview." Journal of Cleaner Production **13**(13-14): 1207-1210.

203) Saling, P., Kicherer, A., Dittrich-Krämer, B., Wittlinger, R., Zombik, W., Schmidt, I., Schrott, W. and Schmidt, S. (2002). "Eco-Efficiency Analysis by BASF: The Method." The International Journal of Life Cycle Assessment **7**(4): 203-218.

204) Sanfélix, J., Mathieux, F., de la Rúa, C., Wolf, M.-A. and Chomkhamsri, K. (2013). "The Enhanced LCA Resources Directory: A Tool Aimed at Improving Life Cycle Thinking Practices." The International Journal of Life Cycle Assessment **18**(1): 273-277.

205) Schmidtmann, U., Kreutz, G., Barkhoff, M., Virkus, K., Stockmann, T., Jovic, M. and Ieee (2009). Material Flow Optimization under Aspects of Energy Efficiency. Iecon: 2009 35th Annual Conference of Ieee Industrial Electronics, Vols 1-6. New York, IEEE**:** 4230-4235.

206) Schneider, J. L., Wilson, A. and Rosenbeck, J. M. (2010). "Pharmaceutical Companies and Sustainability: An Analysis of Corporate Reporting." Benchmarking: An International Journal **17**(3): 421-434.

207) Schwendeman, S. P., Shah, R. B., Bailey, B. A. and Schwendeman, A. S. (2014). "Injectable Controlled Release Depots for Large Molecules." Journal of Controlled Release **190**: 240-253.

208) Sfez, S., Dewulf, J., De Soete, W., Schaubroeck, T., Kralisch, D., Mathieux, F. and De Meester, S. (2016). "Toward a Framework for Resource Efficiency Evaluation: Recommendations for Development & Innovation Projects." Submitted to Resources.

209) Shao, Q., Rowe, R. C. and York, P. (2007). "Investigation of an Artificial Intelligence Technology - Model Trees. Novel Applications for an Immediate Release Tablet Formulation Database." European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences **31**(2): 137-144.

210) Sindelar, G. (2013). "From Cell to Product/Technical and Regulatory Aspects of the Biotechnological Production of Monoclonal Antibodies." Pharmazeutische Industrie **75**(2): 334-339.

211) Sinka, I., Motazedian, F., Cocks, A. and Pitt, K. (2009). "The Effect of Processing Parameters on Pharmaceutical Tablet Properties." Powder Technology **189**(2): 276-284.

212) Soundarrajan, C., Saraswathi, K. and Asiyaparvin, A. (2011). "Piperidone Synthesis Using Amino Acid: A Promising Scope for Green Chemistry." Microchemical Journal **98**(2): 204-206.

213) Statista (2016). "Revenue of the Worldwide Pharmaceutical Market from 2001 to 2014." Retrieved February, 14, 2016, from www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001.

214) Sullivan, S. (2015). "Pharmaceutical Innovation and Greener Chemistry: Celebrating 20 Years of Impact." Chimica Oggi-Chemistry Today **33**(4): 50-51.

215) Szargut, J., Morris, D. R. and Steward, F. R. (1988). Energy Analysis of Thermal, Chemical, and Metallurgical Processes, Springer; 1st edition.

216) Szargut, J., Valero, A. and Stanek, W. (2005). Towards an International Legal Reference Environment.

217) Szekely, G., Jimenez-Solomon, M. F., Marchetti, P., Kim, J. F. and Livingston, A. G. (2014). "Sustainability Assessment of Organic Solvent Nanofiltration: From Fabrication to Application." Green Chemistry **16**(10): 4440-4473.

218) Taelman, S. E., De Meester, S., Schaubroeck, T., Sakshaug, E., Alvarenga, R. A. F. and Dewulf, J. (2014). "Accounting for the Occupation of the Marine Environment as a Natural Resource in Life Cycle Assessment: An Exergy Based Approach." Resources Conservation and Recycling **91**: 1-10.

219) Tang, S. Y., Gurnani, H. and Gupta, D. (2014). "Managing Disruptions in Decentralized Supply Chains with Endogenous Supply Process Reliability." Production and Operations Management **23**(7): 1198-1211.

220) Taormina, R. J. and Gao, J. H. (2013). "Maslow and the Motivation Hierarchy: Measuring Satisfaction of the Needs." Am J Psychol **126**(2): 155-177.

221) Thiel, C. L., Eckelman, M., Guido, R., Huddleston, M., Landis, A. E., Sherman, J., Shrake, S. O., Copley-Woods, N. and Bilec, M. M. (2015). "Environmental Impacts of Surgical Procedures: Life Cycle Assessment of Hysterectomy in the United States." Environmental Science & Technology **49**(3): 1779-1786.

222) Thomas, J. M. and Raja, R. (2005). Designing Catalysts for Clean Technology, Green Chemistry, and Sustainable Development. Annual Review of Materials Research. **35:** 315-350.

223) Pajula, T. (2016). SAMT - Sustainability Assessment Methods and Tools to Support Decision Making in the Process Industries - in a Nutshell Brussels, SPIRE: 42.

224) Tsatsaronis, G. (2007). "Definitions and Nomenclature in Exergy Analysis and Exergoeconomics." Energy **32**(4): 249-253.

225) Tsomaia, N. (2015). "Peptide Therapeutics: Targeting the Undruggable Space." European Journal of Medicinal Chemistry **94**: 459-470.

226) Tucker, J. L. (2006). "Green Chemistry, a Pharmaceutical Perspective." Organic Process Research & Development **10**(2): 315-319.

227) Tucker, J. L. (2015). "Pharmaceutical Green Chemistry at Amgen: Seeing with New Eyes." Aldrichimica Acta **48**(1): 16-17.

228) Umicore (2015). Annual Report 2015 - Umicore - Materials for a Better Life. Brussels, Umicore**:** 192.

229) United Nations (2015). World Population Prospects: The 2015 Revision. New York: United Nations. 1-66.

230) Valero, A. and Martinez, A. (2010). "Inventory of the Exergy Resources on Earth Including Its Mineral Capital." Energy **35**(2): 989-995.

231) Van der Vorst, G., Aelterman, W., De Witte, B., Heirman, B., Van Langenhove, H. and Dewulf, J. (2013). "Reduced Resource Consumption through Three Generations of Galantamine.HBr Synthesis." Green Chemistry **15**(15): 744-748.

232) Van der Vorst, G., Dewulf, J., Aelterman, W., De Witte, B. and Van Langenhove, H. (2009a). "Assessment of the Integral Resource Consumption of Individual Chemical Production Processes in a Multipurpose Pharmaceutical Production Plant: A Complex Task." Industrial & Engineering Chemistry Research **48**(11): 5344-5350.

233) Van der Vorst, G., Dewulf, J., Aelterman, W., De Witte, B. and Van Langenhove, H. (2011). "A Systematic Evaluation of the Resource Consumption of Active Pharmaceutical Ingredient Production at Three Different Levels." Environmental Science & Technology **45**(7): 3040-3046.

234) Van der Vorst, G., Swart, P., Aelterman, W., Van Brecht, A., Graauwmans, E., Van Langenhove, H. and Dewulf, J. (2010). "Resource Consumption of Pharmaceutical Waste Solvent Valorization Alternatives." Resources Conservation and Recycling **54**(12): 1386-1392.

235) Van der Vorst, G., Van Langenhove, H., De Paep, F., Aelterman, W., Dingenen, J. and Dewulf, J. (2009b). "Exergetic Life Cycle Analysis for the Selection of Chromatographic Separation Processes in the Pharmaceutical Industry: Preparative HPLC Versus Preparative Sfc." Green Chemistry **11**(7): 1007-1012.

236) van Oers, L. and Guinee, J. (2016). "The Abiotic Depletion Potential: Background, Updates, and Future." Resources-Basel **5**(1).

237) Vervaet, C. and Remon, J. P. (2005). "Continuous Granulation in the Pharmaceutical Industry." Chemical Engineering Science **60**(14): 3949-3957.

238) Voorhees, K. J. (2015). "ACS GCI Pharmaceutical Roundtable Celebrates 10 Years of Green Chemistry Innovation." Chemical & Engineering News **93**(27): 47-47.

239) Watson, W. J. W. (2012). "How Do the Fine Chemical, Pharmaceutical, and Related Industries Approach Green Chemistry and Sustainability?" Green Chemistry **14**(2): 251-259.

240) Weidema, B. (2012). Ecoinvent V3 - New Dimensions for International LCI Databases. Zürich, Ecoinvent Centre**:** 12.

241) Weidema, B. P., Thrane, M., Christensen, P., Schmidt, J. and Lokke, S. (2008). "Carbon Footprint - a Catalyst for Life Cycle Assessment?" Journal of Industrial Ecology **12**(1): 3-6.

242) Weisberg, S. (1980). Applied Linear Regression, Wiley.

243) Wernet, G., Conradt, S., Isenring, H. P., Jiménez-González, C. and Hungerbühler, K. (2010). "Life Cycle Assessment of Fine Chemical Production: A Case Study of Pharmaceutical Synthesis." The International Journal of Life Cycle Assessment **15**(3): 294-303.

244) Wernet, G., Mutel, C., Hellweg, S. and Hungerbuhler, K. (2011). "The Environmental Importance of Energy Use in Chemical Production." Journal of Industrial Ecology **15**(1): 96-107.

245) Wernet, G., Papadokonstantakis, S., Hellweg, S. and Hungerbuhler, K. (2009). "Bridging Data Gaps in Environmental Assessments: Modelling Impacts of Fine and Basic Chemical Production." Green Chemistry **11**(11): 1826-1831.

246) WHO Collaborating Centre for Drug Statistics Methodology (2015). Guidelines for ATC Classification and DDD Assignment. Oslo, WHO.

247) Wiedmann, T. (2009). "Carbon Footprint and Input-Output Analysis - an Introduction." Economic Systems Research **21**(3): 175-186.

248) Wiedmann, T. and Minx, J. (2007). "A Definition of 'Carbon Footprint'". ISA^{UK} Research & Consulting. Durham, UK, ISA^{UK} Research Report**:** 1-9.

249) Wilson, L. (2010). How to Implement Lean Manufacturing. US, The McGraw-Hill Companies, Inc.

250) Woodley, J. M., Breuer, M. and Mink, D. (2013). "A Future Perspective on the Role of Industrial Biotechnology for Chemicals Production." Chemical Engineering Research and Design **91**(10): 2029-2036.

251) World Business Council on Sustainable Development (2016). Life Cycle Metrics for Chemical Products, WBCSD**:** 119.

252) World Health Organization (2015). Health in 2015: From MDGS, Millennium Development Goals to SDGS, Sustainable Development Goals.**:** 204.

253) Wormer, B. A., Augenstein, V. A., Carpenter, C. L., Burton, P. V., Yokeley, W. T., Prabhu, A. S., Harris, B., Norton, S., Klima, D. A., Lincourt, A. E. and Heniford, B. T. (2013). "The Green Operating Room: Simple Changes to Reduce Cost and Our Carbon Footprint." American Surgeon **79**(7): 666-671.

254) Zhong, S., Geng, Y., Liu, W., Gao, C. and Chen, W. (2016). "A Bibliometric Review on Natural Resource Accounting During 1995–2014." Journal of Cleaner Production **139**: 122-132.

Annexes

A1: Literature review inventory (related to Chapter 2)

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
1	1	Sustainability Assessment of Pharmaceuticals	Wernet et al.	2009	7	Methodological framework with case study	Bridging data gaps in environmental assessments: Modelling impacts of fine and basic chemical production	LCA, midpoints covered	Cradle-to-Gate	34	5	Green Chem.	8.30	Q1
2	1	Sustainability Assessment of Pharmaceuticals	Jiménez-González et al.	2010	6	Review with recommendations	Bioprocesses: Modelling needs for process evaluation and sustainability assessment	Process Analysis and LCA	Cradle-to-Gate	27	5	Comput. Chem. Eng.	2.87	Q1
3	1	Sustainability Assessment of Pharmaceuticals	Schneider et al.	2010	6	Review	Pharmaceutical companies and sustainability: an analysis of corporate reporting	toolbox of social responsibility reporting	N/A	8	1	Benchmark Int J	N/A	N/A
4	1	Sustainability Assessment of Pharmaceuticals	Jiménez-González et al.	2011	5	Perspective with recommendations	Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes	Green Chemistry toolbox	Process Level	102	20	Org. Process Res. Dev.	2.53	Q1
5	1	Sustainability Assessment of Pharmaceuticals	Jiménez-González et al.	2013	3	Methodological framework	Expanding the Boundaries: Developing a Streamlined Tool for Eco-Footprinting of Pharmaceuticals	PMI + LCA	Cradle-to-Gate	19	6	Org. Process Res. Dev.	2.54	Q1
6	1	Sustainability Assessment of Pharmaceuticals	De Soete et al.	2013	3	Case study	Exergetic sustainability assessment of batch versus continuous wet granulation based pharmaceutical tablet manufacturing: a cohesive analysis at three different levels	Combining RE at process level and LCA (CEENE)	Cradle-to-Gate	6	2	Green Chem.	8.30	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
7	1	Sustainability Assessment of Pharmaceuticals	Woodley et al.	2013	3	Perspective with recommendations	A future perspective on the role of industrial biotechnology for chemicals production	N/A	N/A	9	3	Chem. Eng. Res. Des.	2.53	Q2
8	1	Sustainability Assessment of Pharmaceuticals	Szekely et al.	2014	2	Case study	Sustainability assessment of organic solvent nanofiltration: from fabrication to application	CF	Cradle-to-Grave	15	8	Green Chem.	8.30	Q1
9	2	Sustainability Assessment in Healthcare	Briggs et al.	2003	13	Case study	Environmental pollution and the global burden of disease	Health Economics combined with LCA	Cradle-to-Grave	71	5	Br. Med. Bull.	4.42	Q1
10	2	Sustainability Assessment in Healthcare	Martin et al.	2009	7	Case study	Cost-effectiveness of infant vaccination with RIX4414 (Rotarix™) in the UK	Health Economics combined with LCA	Cradle-to-Grave	23	3	Vaccines	3.62	Q2
11	2	Sustainability Assessment in Healthcare	Boholm et al.	2014	2	Case study	Controversy over antibacterial silver: implications for environmental and sustainability assessments	RA, MCA, LCA	Cradle-to-Grave	3	2	J. Clean Prod.	4.17	Q1
12	2	Sustainability Assessment in Healthcare	Carmen Carnero	2015	1	Methodological framework with case study	Assessment of Environmental Sustainability in Health Care Organizations	MCA (CF, material use, toxicity, biodiversity, waste)	Cradle-to-Grave	1	1	Sustainability	0.94	Q3
13	2	Sustainability Assessment in Healthcare	Castro et al. (a)	2015	1	Review	A critical analysis of building sustainability assessment methods for healthcare buildings	BSA	Cradle-to-Cradle	1	1	Environment, Development and Sustainability	0.91	Q2
14	2	Sustainability Assessment in Healthcare	Castro et al. (b)	2015	1	Benchmarking	Development of Benchmarks for Operating Costs and Resources Consumption to be Used in Healthcare	Resource consumption, BSA	Cradle-to-Cradle	0	0	Sustainability	0.94	Q3

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
							Building Sustainability Assessment Methods							
15	2	Sustainability Assessment in Healthcare	Debaveye et al.	2016	0	Methodological framework	Human health benefits and burdens of a pharmaceutical treatment: Discussion of a conceptual integrated approach	Health Economics combined with LCA	Cradle-to-Grave	0	0	Environ. Res.	4.37	Q1
16	2	Sustainability Assessment in Healthcare	Marsch et al.	2016	0	Methodological framework	Expanding Health Technology Assessments to Include Effects on the Environment	Health Economics combined with LCA	Cradle-to-Grave	0	0	Value in Health	3.37	Q1
17	3	Life Cycle Assessment of Pharmaceuticals	Jiménez-González et al.	2000	16	PhD Research	Life Cycle Assessment in Pharmaceutical Applications	Green Chemistry + LCA Toolbox	N/A	N/A	N/A	N/A	N/A	N/A
18	3	Life Cycle Assessment of Pharmaceuticals	Jiménez-González et al.	2004	12	Case study	Cradle-to-gate life cycle inventory and assessment of pharmaceutical compounds	LCA, most midpoints covered	Gate-to-Gate	79	7	Int. J. Life Cycle Assess.	4.38	Q1
19	3	Life Cycle Assessment of Pharmaceuticals	Curzons et al.	2007	9	Methodological framework	Fast life cycle assessment of synthetic chemistry (FLASC™) tool	FLASC™, process-oriented metrics	Cradle-to-Gate	42	5	Int. J. Life Cycle Assess.	4.38	Q1
20	3	Life Cycle Assessment of Pharmaceuticals	Kim et al.	2009	7	Methodological framework with case study	Enzymes for pharmaceutical applications-a cradle-to-gate life cycle assessment	FLASC™, nonrenewable energy consumption, global warming, acidification, eutrophication, and photochemical smog formation	Cradle-to-Grave	19	3	Int. J. Life Cycle Assess.	4.38	Q1

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	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
21	3	Life Cycle Assessment of Pharmaceuticals	Wernet et al.	2010	6	Case study	Life cycle assessment of fine chemical production: a case study of pharmaceutical synthesis	CED, GWP, EI99, ES2006, TRACI	Cradle-to-Gate	38	6	Int. J. Life Cycle Assess.	4.38	Q1
22	3	Life Cycle Assessment of Pharmaceuticals	Igos et al.	2012	4	Benchmarking	Is it better to remove pharmaceuticals in decentralized or conventional wastewater treatment plants? A life cycle assessment comparison	LCA, most midpoints covered	Cradle-to-Grave	9	2	Sci. Total Environ.	4.41	Q1
23	3	Life Cycle Assessment of Pharmaceuticals	Alfonsín et al.	2014	2	Methodological framework with case study	PPCPs in wastewater – Update and calculation of characterization factors for their inclusion in LCA studies	USEtox and USES-LCA 2.0	Gate-to-Cradle	1	1	J. Clean Prod.	4.17	Q1
24	3	Life Cycle Assessment of Pharmaceuticals	De Soete et al.	2014	2	Methodological framework with case study	Environmental Sustainability Assessments of Pharmaceuticals: An Emerging Need for Simplification in Life Cycle Assessments	Combining resource efficiency at process level and LCA (CEENE)	Cradle-to-Gate	0	0	Environ. Sci. Technol.	6.33	Q1
25	3	Life Cycle Assessment of Pharmaceuticals	Jiménez-González et al.	2014	2	Review	The evolution of life cycle assessment in pharmaceutical and chemical applications - a perspective	LCA, midpoints covered	Cradle-to-Gate	5	3	Green Chem.	8.30	Q1
26	3	Life Cycle Assessment of Pharmaceuticals	Perez-Lopez et al.	2014	2	Case study	Life cycle assessment of the production of bioactive compounds from	LCA	Cradle-to-Gate	4	2	J. Clean Prod.	4.17	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
							Tetraselmis suecica at pilot scale							
27	3	Life Cycle Assessment of Pharmaceuticals	Brunet et al.	2014	2	Methodological framework with case study	Combined simulation-optimization methodology to reduce the environmental impact of pharmaceutical processes: application to the production of Penicillin V	Combining process analysis and LCA (CML + EI99)	Cradle-to-Gate	1	1	J. Clean Prod.	4.17	Q1
28	3	Life Cycle Assessment of Pharmaceuticals	Ramasamy et al.	2014	2	Review with recommendations	Life cycle assessment as a tool to support decisionmaking in the biopharmaceutical industry: Considerations and challenges	LCA	Cradle-to-Gate	0	0	Food Bioprod. Process.	2.82	Q2
29	3	Life Cycle Assessment of Pharmaceuticals	Ott et al.	2014	2	Case study	Life Cycle Analysis within Pharmaceutical Process Optimization and Intensification: Case Study of Active Pharmaceutical Ingredient Production	Combining process analysis and LCA (ReCiPe)	Cradle-to-Gate	3	2	ChemSusChem	8.65	Q1
30	3	Life Cycle Assessment of Pharmaceuticals	Ott et al.	2015	1	Case study	Life cycle assessment of multi-step rufinamide synthesis – from isolated reactions in batch to continuous microreactor networks	Combining process analysis and LCA (ReCiPe)	Cradle-to-Gate	0	0	Green Chem.	8.30	Q1

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	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
31	3	Life Cycle Assessment of Pharmaceuticals	Cespi et al.	2015	1	Methodological framework with case study	Life cycle inventory improvement in the pharmaceutical sector: assessment of the sustainability combining PMI and LCA tools	PMI + LCA	Cradle-to-Gate	0	0	Green Chem.	8.30	Q1
32	3	Life Cycle Assessment of Pharmaceuticals	Kralisch et al.	2015	1	Review with recommendations	Rules and benefits of Life Cycle Assessment in green chemical process and synthesis design: a tutorial review	LCA	Cradle-to-Cradle	7	7	Green Chem.	8.30	Q1
33	4	Life Cycle Assessment in Healthcare	Campion et al.	2012	4	Case study	Life cycle assessment perspectives on delivering an infant in the US	TRACI	Cradle-to-Grave	7	2	Sci. Total Environ.	4.42	Q1
34	4	Life Cycle Assessment in Healthcare	Thiel et al.	2015	1	Review with recommendations	Environmental Impacts of Surgical Procedures: Life Cycle Assessment of Hysterectomy in the United States	Hybrid LCA		1	1	Environ. Sci. Technol.	6.33	Q1
35	5	Green Chemistry related to Pharmaceuticals	Curzons et al.	1999	17	Methodological framework	Solvent Selection Guide: A Guide to the Integration of Environmental, Health and Safety Criteria into the Selection of Solvents	Green Chemistry toolbox	Process Level	10	1	Clean Products and Processes	1.93	Q1
36	5	Green Chemistry related to Pharmaceuticals	Curzons et al.	2001	15	Methodological framework	So You Think Your Process Is Green, How Do You Know?-Using Principles of Sustainability to Determine What Is Green-a Corporate Perspective.	Green Chemistry + LCA Toolbox	Cradle-to-Gate	156	11	Green Chem.	8.30	Q1

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	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
37	5	Green Chemistry related to Pharmaceuticals	Constable et al.	2002	14	Review with recommendations	Metrics to 'green' chemistry - which are the best?	Process Analysis	Gate-to-Gate	215	15	Green Chem.	8.30	Q1
38	5	Green Chemistry related to Pharmaceuticals	Haswell et al.	2003	13	Review	Green chemistry: synthesis in micro reactors	Green Chemistry toolbox	Process Level	111	9	Green Chem.	8.30	Q1
39	5	Green Chemistry related to Pharmaceuticals	Nisiwaki	2003	13	Review	Green chemistry in process research and development in pharmaceutical industry	Green Chemistry toolbox	Process Level	1	0	J. Synth. Org. Chem. Jpn.	0.71	Q4
40	5	Green Chemistry related to Pharmaceuticals	Thomas et al.	2005	11	Methodological framework with case study	Designing catalysts for clean technology, green chemistry, and sustainable development	Green Chemistry toolbox	Process Level	54	5	Ann. Rev. Mater. Res.	17.98	Q1
41	5	Green Chemistry related to Pharmaceuticals	Koel et al.	2006	10	Case study	Application of the principles of green chemistry in analytical chemistry	Green Chemistry toolbox	Process Level	66	7	Pure Appl. Chem.	3.20	Q2
42	5	Green Chemistry related to Pharmaceuticals	Tucker	2006	10	Review with recommendations	Green chemistry, a pharmaceutical perspective	Green Chemistry toolbox	Process Level	87	9	Org. Process Res. Dev.	2.53	Q1
43	5	Green Chemistry related to Pharmaceuticals	Constable et al.	2007	9	Perspective with recommendations	Key green chemistry research areas - a perspective from pharmaceutical manufacturers	Green Chemistry toolbox	Process Level	437	49	Green Chem.	8.30	Q1
44	5	Green Chemistry related to Pharmaceuticals	Fortunak et al.	2007	9	Review	Strength and honor through the pharmaceutical industry's embrace of green chemistry?	Green Chemistry toolbox	Process Level	1	0	Curr. Opin. Drug. Disc	5.12	Q1
45	5	Green Chemistry related to Pharmaceuticals	Khetan et al.	2007	9	Review with recommendations	Human pharmaceuticals in the aquatic environment: A challenge to green chemistry	Green Chemistry toolbox	Cradle-to-Grave	326	36	Chem. Rev.	50.68	Q1

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	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
46	5	Green Chemistry related to Pharmaceuticals	Kuemmerer	2007	9	Review	Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry	Green Chemistry toolbox	Process Level	51	6	Green Chem.	8.30	Q1
47	5	Green Chemistry related to Pharmaceuticals	Alfonsi et al.	2008	8	Methodological framework	Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation	Green Chemistry toolbox	Process Level	309	39	Green Chem.	8.30	Q1
48	5	Green Chemistry related to Pharmaceuticals	Cue et al.	2009	7	Review	Green process chemistry in the pharmaceutical industry	Green Chemistry toolbox	Process Level	21	3	Green Chem. Lett. Rev.	1.52	Q3
49	5	Green Chemistry related to Pharmaceuticals	Fortunak	2009	7	Review	Current and future impact of green chemistry on the pharmaceutical industry	Green Chemistry toolbox	Process Level	6	1	Future Med. Chem.	3.79	Q1
50	5	Green Chemistry related to Pharmaceuticals	Garcia-Reyes et al.	2009	7	Case study	Flow-Through Solid-Phase Spectroscopy: A Contribution to Green Analytical Chemistry	Green Chemistry toolbox	Process Level	4	1	Spectr. Lett.	0.85	Q4
51	5	Green Chemistry related to Pharmaceuticals	Molina-Diaz et al.	2010	6	Case study	How green chemistry can contribute to pharmaceutical industry sustainability: Accomplishments and opportunites	Green Chemistry toolbox	Process Level	13	2	Trac-Trends Anal. Chem.	6.93	Q1
52	5	Green Chemistry related to Pharmaceuticals	Broxterman et al.	2011	5	Methodological framework	Pharma and suppliers collaborating on Green Chemistry Launch of PMI tool	PMI Toolbox	Process Level	3	1	Chim. Oggi-Chem. Today	0.41	Q4

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	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
53	5	Green Chemistry related to Pharmaceuticals	Hartman et al.	2011	5	Case study	Analytical Method Volume Intensity (AMVI): A green chemistry metric for HPLC methodology in the pharmaceutical industry	Green Chemistry toolbox	Process Level	11	2	Green Chem.	8.30	Q1
54	5	Green Chemistry related to Pharmaceuticals	Wernet et al.	2011	5	Perspective with recommendations	The Environmental Importance of Energy Use in Chemical Production	LCA	Cradle-to-Gate	10	2	J. Ind. Ecol.	3.70	Q1
55	5	Green Chemistry related to Pharmaceuticals	Jiménez-González et al.	2011	5	Perspective with recommendations	Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers	N/A	N/A	90	18	Org. Process Res. Dev.	2.53	Q1
56	5	Green Chemistry related to Pharmaceuticals	Joshi et al.	2011	5	Review with recommendations	Green Chemistry: Need of the Hour	Green Chemistry toolbox	Process Level	0	0	Indian J. Pharm. Educ. Res.	0.38	Q4
57	5	Green Chemistry related to Pharmaceuticals	Soundarrajan et al.	2011	5	Case study	Piperidone synthesis using amino acid: A promising scope for green chemistry	Green Chemistry toolbox	Process Level	0	0	Microchem J.	3.05	Q2
58	5	Green Chemistry related to Pharmaceuticals	Kaur et al.	2012	4	Case study	Comparative Study of Various Green Chemistry Approaches for the Efficient Synthesis of 1,4-Dihydropyridines	Green Chemistry toolbox	Process Level	8	2	Asian J. Chem.	0.36	Q4
59	5	Green Chemistry related to Pharmaceuticals	Ley	2012	4	Methodological framework	On being green: Can flow chemistry help?	Green Chemistry toolbox	Process Level	74	19	Chem. Rec.	5.50	Q1
60	5	Green Chemistry related to Pharmaceuticals	Watson	2012	4	Review with recommendations	How do the fine chemical, pharmaceutical, and related	Green Chemistry toolbox	Process Level	51	13	Green Chem.	8.30	Q1

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	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
							industries approach green chemistry and sustainability?							
61	5	Green Chemistry related to Pharmaceuticals	Ciriminna	2013	3	Review with recommendations	Green Chemistry in the Fine Chemicals and Pharmaceutical Industries	Green Chemistry toolbox	Process Level	13	4	Org. Process Res. Dev.	2.53	Q1
62	5	Green Chemistry related to Pharmaceuticals	Dunn	2013	3	Perspective with recommendations	Pharmaceutical Green Chemistry process changes - how long does ittake to obtain regulatory approval?	Green Chemistry + LCA Toolbox	Cradle-to-Gate	5	2	Green Chem.	8.30	Q1
63	5	Green Chemistry related to Pharmaceuticals	Federsel	2013	3	Perspective with recommendations	En route to full implementation: driving the green chemistry agenda in the pharmaceutical industry	PMI Toolbox	Cradle-to-Gate	7	2	Green Chem.	8.30	Q1
64	5	Green Chemistry related to Pharmaceuticals	Leahy et al.	2013	3	Perspective with recommendations	Seven Important Elements for an Effective Green Chemistry Program: An IQ Consortium Perspective	Green Chemistry toolbox	Process Level	11	4	Org. Process Res. Dev.	2.53	Q1
65	5	Green Chemistry related to Pharmaceuticals	Osorio et al.	2014	2	Case study	Photochemical derivatization of amitriptyline using a green chemistry approach: fluorimetric determination and photochemical reaction mechanism	Green Chemistry toolbox	Process Level	0	0	Anal. Methods	1.84	Q2
66	5	Green Chemistry related to Pharmaceuticals	Rastogi et al.	2014	2	Methodological framework	Designing green derivatives of beta-blocker Metoprolol: A tiered approach for green and	Green Chemistry Toolbox and QSAR	Process Level	5	3	Chemosphere	3.85	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
							sustainable pharmacy and chemistry							
67	5	Green Chemistry related to Pharmaceuticals	Banimostafa et al.	2015	1	Case study	Retrofit design of a pharmaceutical batch process considering "green chemistry and engineering" principles	LCA	Cradle-to-Gate	0	0	AICHE J.	2.75	Q1
68	5	Green Chemistry related to Pharmaceuticals	DeVito et al.	2015	1	Case study	Can pollutant release and transfer registers (PRTRs) be used to assess implementation and effectiveness of green chemistry practices? A case study involving the Toxics Release Inventory (TRI) and pharmaceutical manufacturers	Green Chemistry toolbox	Process Level	0	0	Green Chem.	8.30	Q1
69	5	Green Chemistry related to Pharmaceuticals	Gupta et al.	2015	1	Perspective	Green chemistry approaches as sustainable alternatives to conventional strategies in the pharmaceutical industry	Green Chemistry toolbox	Process Level	0	0	RSC Adv.	3.91	Q1
70	5	Green Chemistry related to Pharmaceuticals	M'Hamed	2015	1	Perspective	Green chemistry approaches as sustainable alternatives to conventional strategies in the pharmaceutical industry	Green Chemistry toolbox	Process Level	0	0	Synth. Commun.	0.99	Q3
71	5	Green Chemistry related to Pharmaceuticals	Roschangar et al.	2015	1	Methodological framework with case study	Overcoming barriers to green chemistry in the pharmaceutical industry - the	Green Chemistry toolbox	Process Level	7	7	Green Chem.	8.30	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
							Green Aspiration Level™ concept							
72	5	Green Chemistry related to Pharmaceuticals	Sullivan	2015	1	Review	Pharmaceutical innovation and greener chemistry: Celebrating 20 years of impact	Green Chemistry toolbox	Process Level	0	0	Chim. Oggi-Chem. Today	0.41	Q4
73	5	Green Chemistry related to Pharmaceuticals	Tucker	2015	1	Methodological framework	Pharmaceutical Green Chemistry at Amgen: Seeing with New Eyes	Green Chemistry toolbox	Process Level	0	0	Aldrichimica Acta	17.08	Q1
74	5	Green Chemistry related to Pharmaceuticals	Voorhees	2015	1	Perspective with recommendations	ACS GCI Pharmaceutical Roundtable Celebrates 10 Years Of Green Chemistry Innovation	Green Chemistry toolbox	Process Level	0	0	Chem. Eng. News	0.27	Q4
75	5	Green Chemistry related to Pharmaceuticals	Gallou et al.	2016	0	Case study	Surfactant technology applied toward an active pharmaceutical ingredient: more than a simple green chemistry advance	Green Chemistry toolbox	Process Level	1	0	Green Chem.	8.30	Q1
76	5	Green Chemistry related to Pharmaceuticals	Borukhova et al.	2016	0	Case study	Hydrogen Chloride Gas in Solvent-Free Continuous Conversion of Alcohols to Chlorides in Microflow	Green Chemistry toolbox	Process Level	0	0	Org. Process Res. Dev.	2.53	Q1
77	6	Resource Consumption related to Pharmaceuticals	Van der Vorst et al.	2009	7	Case study	Exergetic life cycle analysis for the selection of chromatographic separation processes in the pharmaceutical industry: preparative HPLC versus preparative SFC	Combining RE at process level and LCA (CEENE)	Cradle-to-Gate	26	4	Green Chem.	8.30	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
78	6	Resource Consumption related to Pharmaceuticals	Van der Vorst et al.	2009	7	Methodological framework with case study	Assessment of the Integral Resource Consumption of Individual Chemical Production Processes in a Multipurpose Pharmaceutical Production Plant: A Complex Task	Combining RE at process level and LCA (CEENE)	Cradle-to-Gate	11	2	Ind. Eng. Chem. Res.	2.74	Q1
79	6	Resource Consumption related to Pharmaceuticals	Van der Vorst et al.	2010	6	Case study	Resource consumption of pharmaceutical waste solvent valorization alternatives	Resource efficiency analysis	Cradle-to-Gate	4	1	Resour. Conserv. Recycl.	3.28	Q2
80	6	Resource Consumption related to Pharmaceuticals	Van der Vorst et al.	2011	5	Methodological framework	A Systematic Evaluation of the Resource Consumption of Active Pharmaceutical Ingredient Production at Three Different Levels	Combining RE at process level and LCA (CEENE)	Cradle-to-Gate	10	2	Environ. Sci. Technol.	6.33	Q1
81	6	Resource Consumption related to Pharmaceuticals	Van der Vorst et al.	2013	3	Case study	Reduced resource consumption through three generations of Galantamine-HBr synthesis	Combining RE at process level and LCA (CEENE)	Cradle-to-Gate	6	2	Green Chem.	8.30	Q1
82	6	Resource Consumption related to Pharmaceuticals	De Soete et al.	2014	2	Case study	Environmental resource footprinting of drug manufacturing: Effects of scale-up and tablet dosage	Combining RE at process level and LCA (CEENE)	Cradle-to-Gate	1	1	Resour. Conserv. Recycl.	3.28	Q2
83	7	Resource Consumption related to Healthcare	Hatoum et al.	1998	18	Case study	Insomnia, health-related quality of life and healthcare resource consumption - A study of managed-	Resource efficiency analysis	Process Level	91	5	Pharmacoeconomics	2.57	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
							care organisation enrollees							
84	7	Resource Consumption related to Healthcare	Optenberg	2002	14	Case study	Antidepressant selection, healthcare resource consumption and costs in a large workplace environment - US and Canadian perspectives	Resource efficiency analysis	Process Level	1	0	Clin. Drug Invest.	1.61	Q3
85	7	Resource Consumption related to Healthcare	Alvarez et al.	2004	12	Case study	Socioeconomic status and resource consumption in primary care	Resource efficiency analysis	Process Level	3	0	An. Pediatr.	0.83	Q4
86	7	Resource Consumption related to Healthcare	Daskalaki et al.	2007	9	Case study	Resource consumption in the infection control management of pertussis exposure among Healthcare workers in Pediatrics	Resource efficiency analysis	Process Level	14	2	Infect. Control Hosp. Epidemiol.	4.50	Q1
87	7	Resource Consumption related to Healthcare	Manca	2008	8	Case study	Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial)	Resource efficiency analysis	Process Level	59	7	Eur. J. Pain	3.51	Q2
88	7	Resource Consumption related to Healthcare	Leekha	2009	7	Case study	Epidemiology and Control of Pertussis Outbreaks in a Tertiary Care Center and the Resource Consumption Associated With These Outbreaks	Resource efficiency analysis	Process Level	10	1	Infect. Control Hosp. Epidemiol.	4.50	Q1

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
89	7	Resource Consumption related to Healthcare	Gonzalez-Cortes et al.	2011	5	Case study	Prolonged stay in pediatric intensive care units: mortality and healthcare resource consumption	Resource efficiency analysis	Process Level	6	1	Med. Intensiv.	1.33	Q4
90	7	Resource Consumption related to Healthcare	Gagliardino et al.	2012	4	Case study	Patients' education, and its impact on care outcomes, resource consumption and working conditions: Data from the International Diabetes Management Practices Study (IDMPS)	Resource efficiency analysis	Process Level	16	4	Diabetes Metab.	3.27	Q2
91	7	Resource Consumption related to Healthcare	Polatli et al.	2012	4	Case study	Chronic obstructive pulmonary disease and associated healthcare resource consumption in the Middle East and North Africa: The BREATHE study	Resource efficiency analysis	Process Level	8	2	Respir. Med.	3.09	Q2
92	7	Resource Consumption related to Healthcare	Roggeri et al.	2014	2	Case study	Direct healthcare costs and resource consumption after acute coronary syndrome: a real-life analysis of an Italian subpopulation	Resource efficiency analysis	Process Level	1	1	Eur. J. Prev. Cardiol.	3.38	Q2
93	7	Resource Consumption related to Healthcare	Castro et al.	2015	1	Methodological framework	Development of Benchmarks for Operating Costs and Resources Consumption to be Used in Healthcare Building Sustainability Assessment Methods	BSA	Gate-to-Gate	0	0	Sustainability	0.94	Q3

Annex A1: Literature review inventory related to Chapter 2

	TAG	Criterion	Authors	Year	Years Published	Publication Type	Topic	Impact Assessment Method	System Boundary	Citations	Citations per year	Journal (ISO)	IF	Q
94	7	Resource Consumption related to Healthcare	Martyn et al.	2015	1	Case study	Reduction in hospital costs and resource consumption associated with the use of advanced topical hemostats during inpatient procedures	Resource efficiency analysis	Process Level	0	0	J. Med. Econ.	1.66	Q1
95	8	Carbon Footprinting of Pharmaceuticals	Connor et al.	2010	6	Case study	The carbon footprint of a renal service in the United Kingdom	CF	Cradle-to-Grave	16	3	QJM-An Int. J. Med.	2.62	Q1
96	8	Carbon Footprinting of Pharmaceuticals	Gatenby	2011	5	Case study	Modelling the carbon footprint of reflux control	CF	Cradle-to-Grave	5	1	Int. J. Surg.	1.80	Q2
97	8	Carbon Footprinting of Pharmaceuticals	Lim et al.	2013	3	Case study	The carbon footprint of an Australian satellite haemodialysis unit	CF	Cradle-to-Grave	4	1	Aust. Health Rev.	0.96	Q4
98	9	Carbon Footprinting in Healthcare	Connor et al.	2011	5	Case study	The carbon footprints of home and in-center maintenance hemodialysis in the United Kingdom	CF	Cradle-to-Grave	25	5	Hemodial. Int.	1.36	Q3
99	9	Carbon Footprinting in Healthcare	Wormer et al.	2013	3	Review with recommendations	The Green Operating Room: Simple Changes to Reduce Cost and Our Carbon Footprint	CF	Cradle-to-Grave	5	2	Am. Surg.	1.11	Q4
100	9	Carbon Footprinting in Healthcare	Holmer et al.	2014	2	Perspective with recommendations	Carbon Footprint of Telemedicine Solutions - Unexplored Opportunity for Reducing Carbon Emissions in the Health Sector	CF	Cradle-to-Grave	1	1	PLoS One	3.70	Q1
101	9	Carbon Footprinting in Healthcare	Pollard et al.	2014	2	Review with recommendations	The carbon footprint of acute care: how energy intensive is critical care?	CF	Cradle-to-Gate	0	0	Public Health	1.62	Q2

Annex A1: Literature review inventory related to Chapter 2

A2: TRAMACET® production processes (related to Chapter 4)

Consecutive batch core processes (α level)

ID TAG	PROCESS
α-1	DISPENSING
α-1.1	Weighing & Bin Filling
α-1.2	Pre-Mixing
α-2	GRANULATION
α-2.1	Granulation Solution Preparation
α-2.2	Equipment Conditioning
α-2.3	Load Raw Materials
α-2.4	Dry Mixing
α-2.5	Spraying
α-2.6	Drying
α-2.7	Sizing and External Phase Adding
α-3	MIXING
α-3.1	Mixing (Press Preparation)
α-4	COMPRESSION
α-4.1	Compression
α-5	COATING
α-5.1	Coating Solution Preparation
α-5.2	Warm-Up
α-5.3	Spraying
α-5.4	Drying
α-5.5	Cooling
α-5.6	Wax Addition

α-6	PACKAGING
α-6.1	Packaging

Supporting core processes (β level)

ID TAG	PROCESS
β-1	TRANSPORT
β-1.1	Primary Transport
β-1.2	Secondary Transport
β-2	REVERSE OSMOSIS
β-2.1	Reverse Osmosis
β-3	STEAM GENERATION
β-3.1	Steam Generation
β-3.2	Water Production (Cold, 30°C)
β-3.3	Water Production (Hot, 50°C)
β-4	AIR COMPRESSION
β-4.1	Air Compression
β-5	WASTEWATER TREATMENT
β-5.1	Wastewater Treatment
β-6	AIR TREATMENT
β-6.1	Air Treatment

Main industrial processes (γ level)

ID TAG	PROCESS
γ-1	MATERIAL PRODUCTION & TRANSPORT
γ-1.1	API Production & Transport
γ-1.2	Excipient Production & Transport
γ-1.3	Packaging Material Production & Transport
γ-1.4	Detergent Production & Transport
γ-2	TAP WATER PRODUCTION
γ-2.1	Tap Water Production

γ-3	ELECTRICITY PRODUCTION
γ-3.1	CHP
γ-3.2	Italian Network Electricity Production
γ-4	SLUDGE TREATMENT
γ-4.1	Incineration & residual landfilling
γ-5	SOLID WASTE TREATMENT
γ-5.1	Recycling

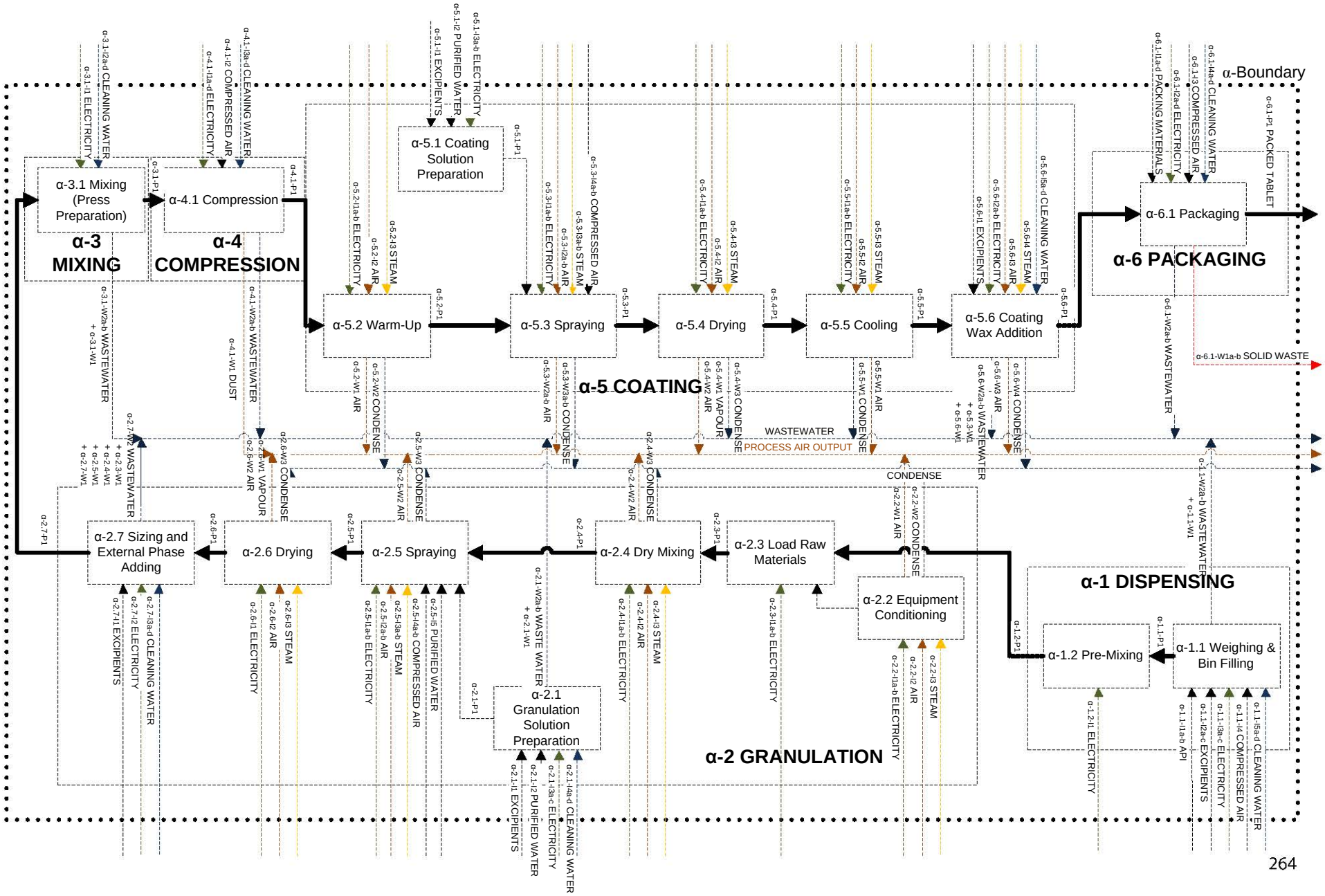
Consecutive continuous core processes (α level)

ID TAG	PROCESS
α-1	DISPENSING
α-1.1	Weighing & Bin Filling
α-1.2	Pre-Mixing
α-2	GRANULATION
α-2.1	Granulation Solution Preparation
α-2.2	Conditioning & Feeding
α-2.3	Screw Granulation
α-2.4	Drying
α-2.5	Sizing and External Phase Adding
α-3	MIXING
α-3.1	Mixing (Press Preparation)
α-4	COMPRESSION
α-4.1	Compression
α-5	COATING
α-5.1	Coating Solution Preparation
α-5.2	Warm-Up
α-5.3	Spraying
α-5.4	Drying
α-5.5	Cooling
α-5.6	Wax Addition
α-6	PACKAGING

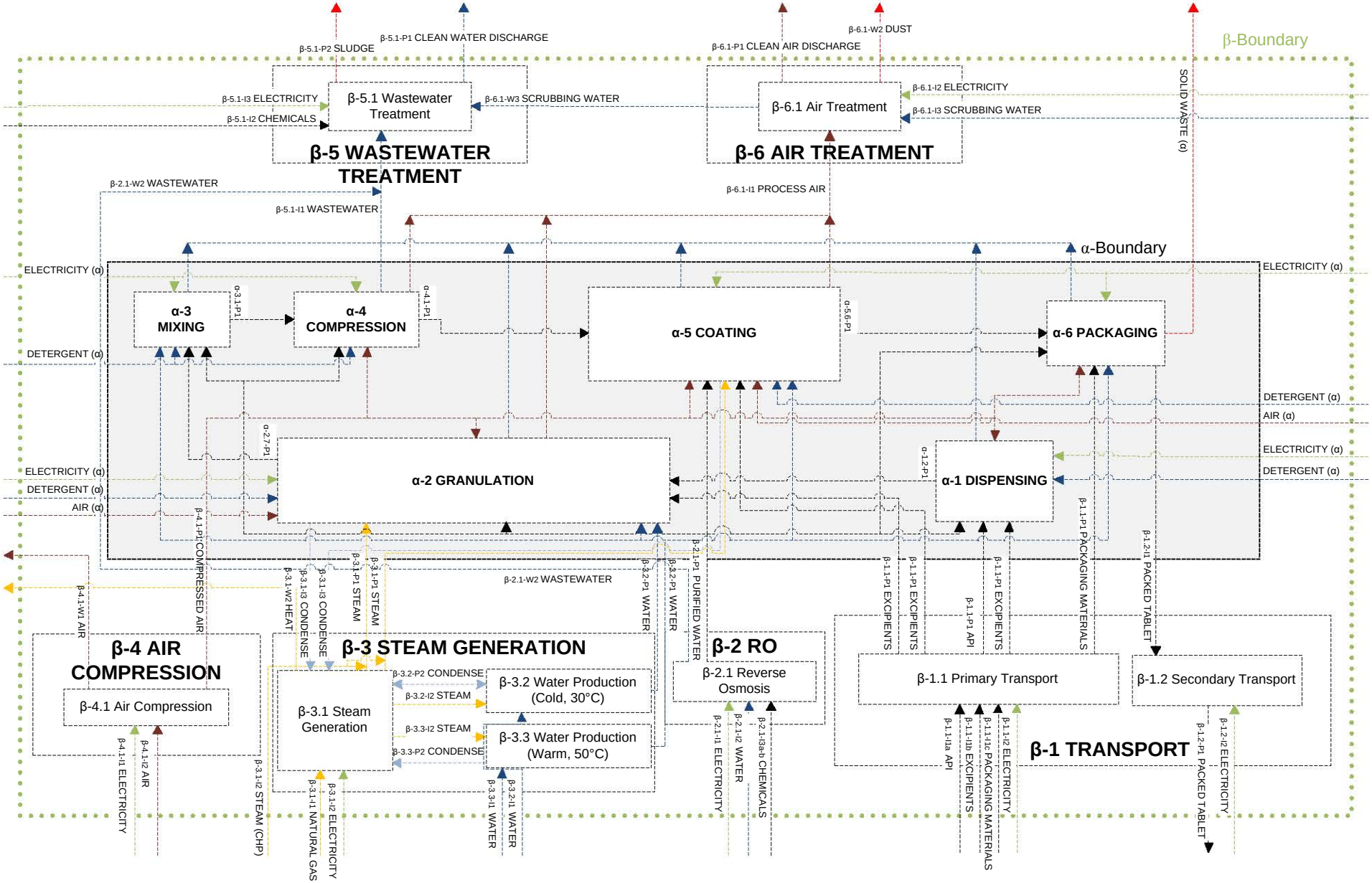
α-6.1	Packaging

A3: Detailed flowcharts of the TRAMACET® product systems (related to Chapter 4)

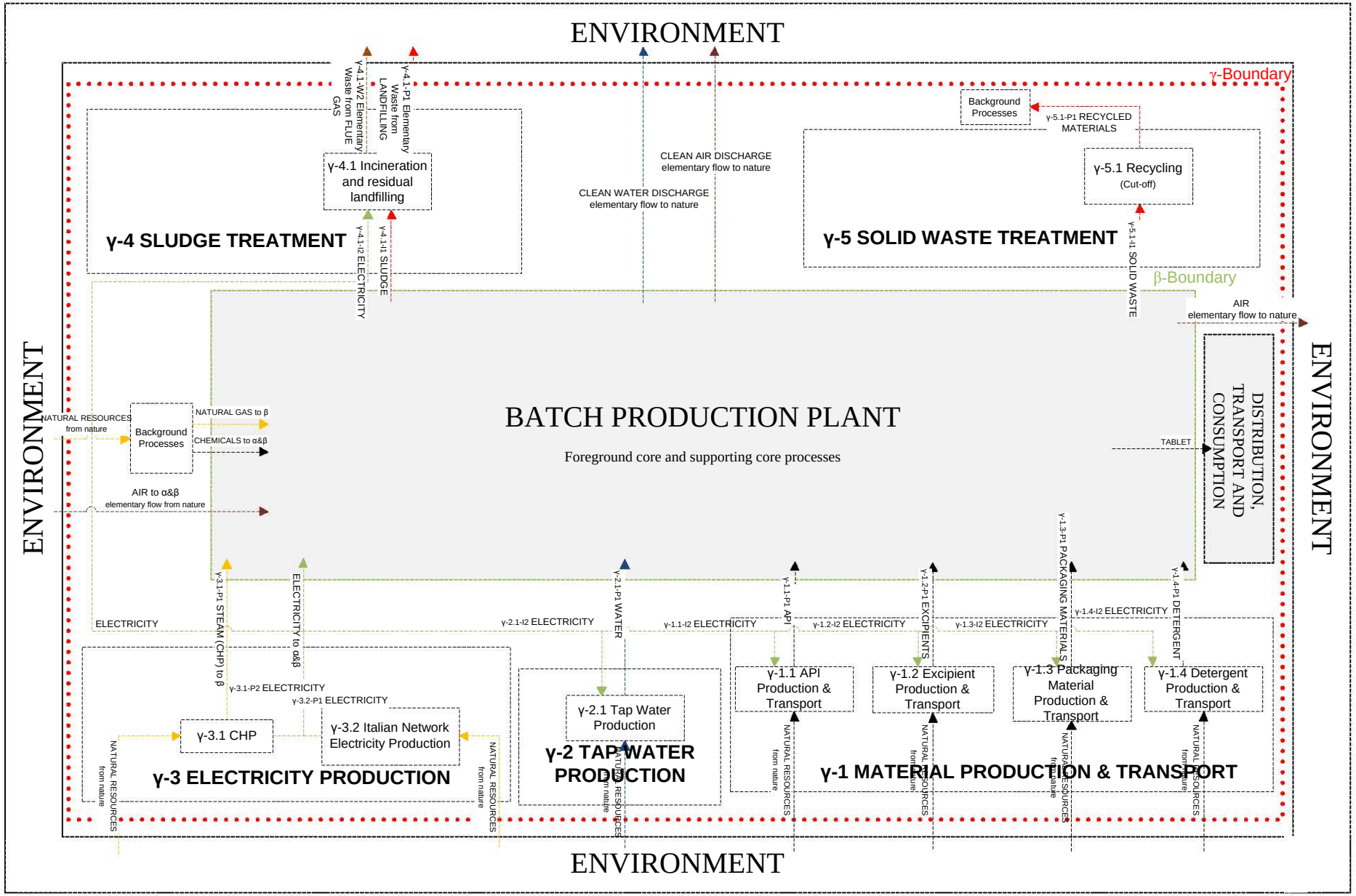
Annex A3.1: Batch Flowchart TRAMACET® α system (related to Chapter 4)



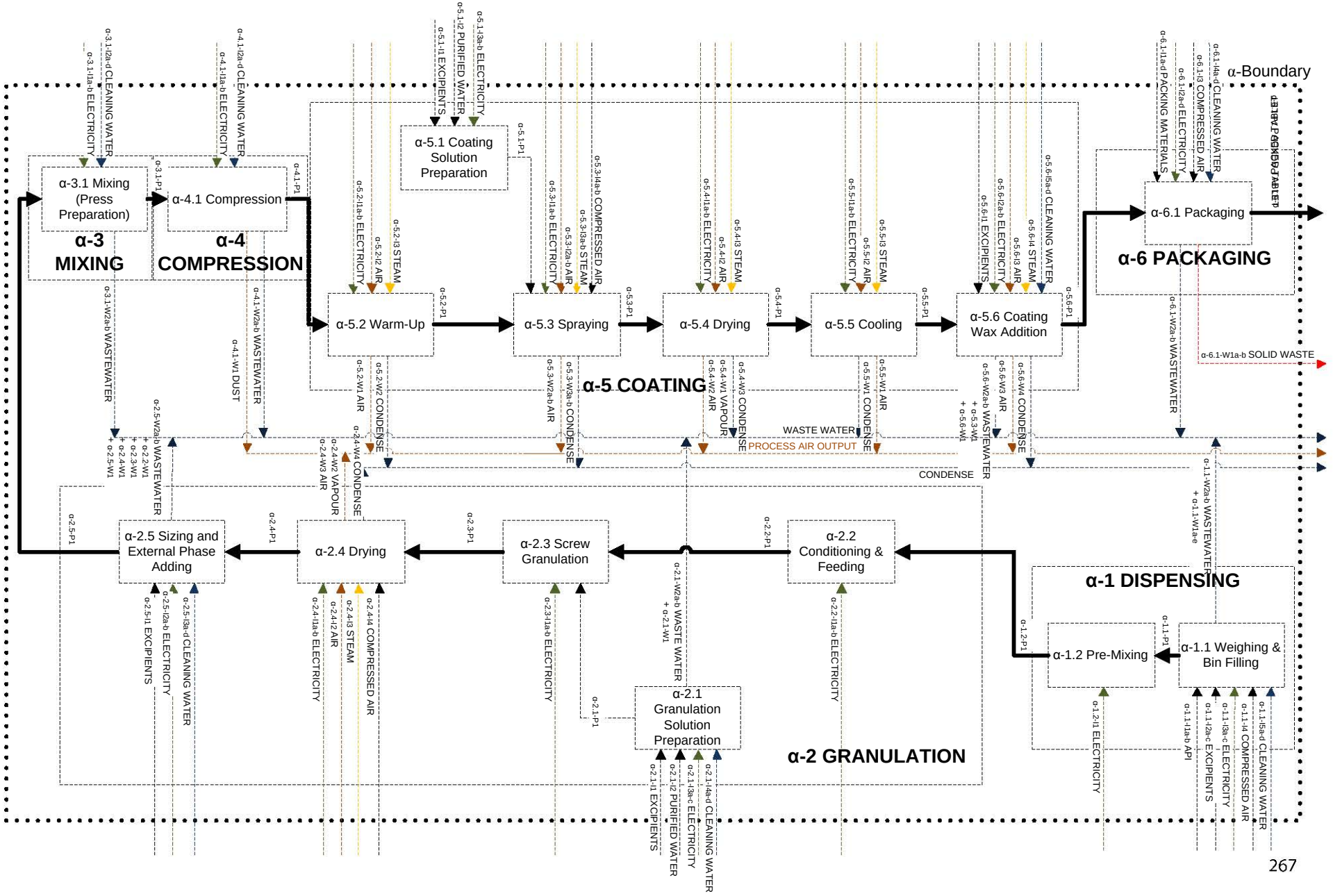
Annex A3.2: Batch Flowchart TRAMACET® β system (related to Chapter 4)



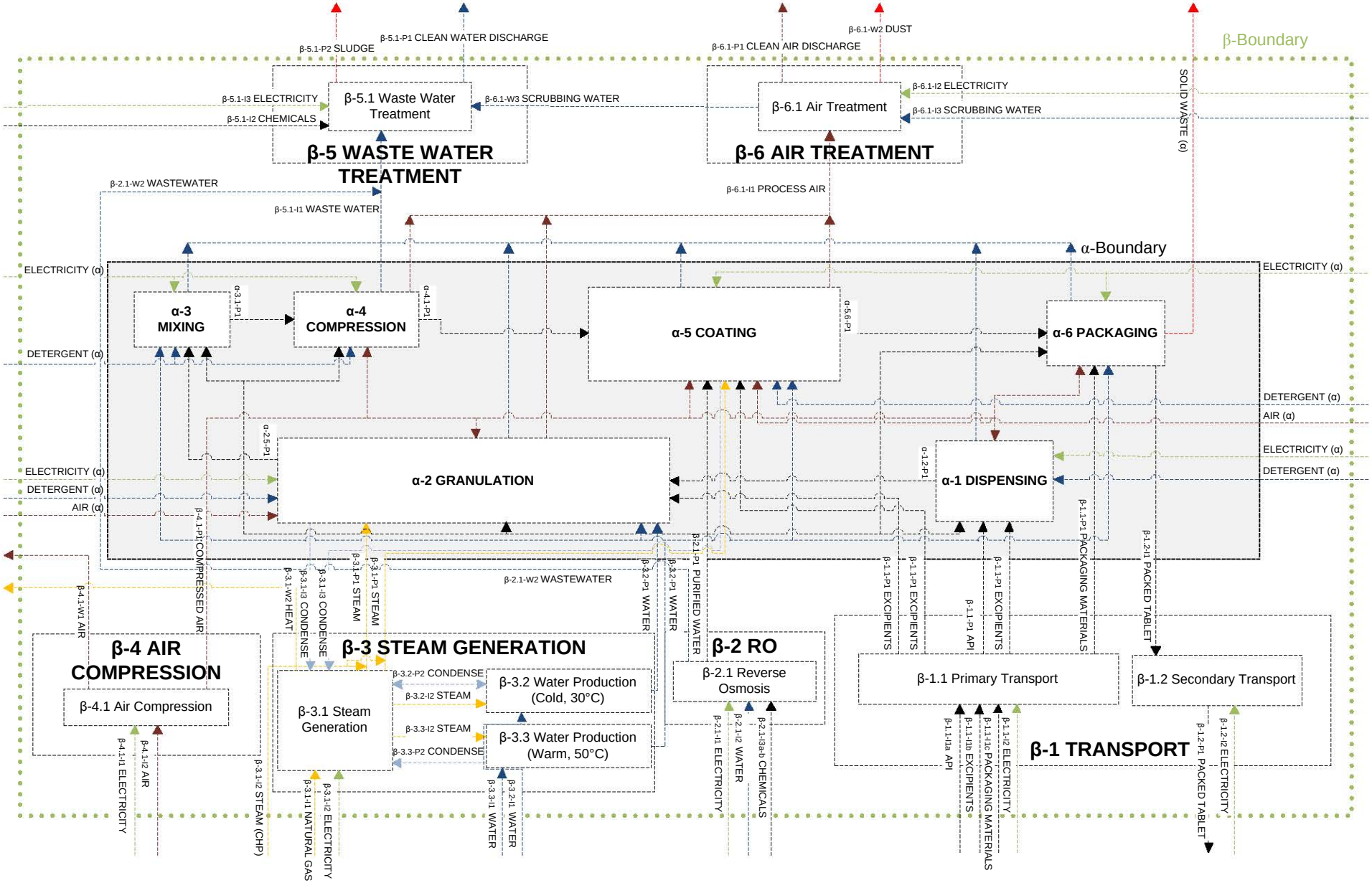
Annex A3.3: Batch Flowchart TRAMACET® γ system (related to Chapter 4)



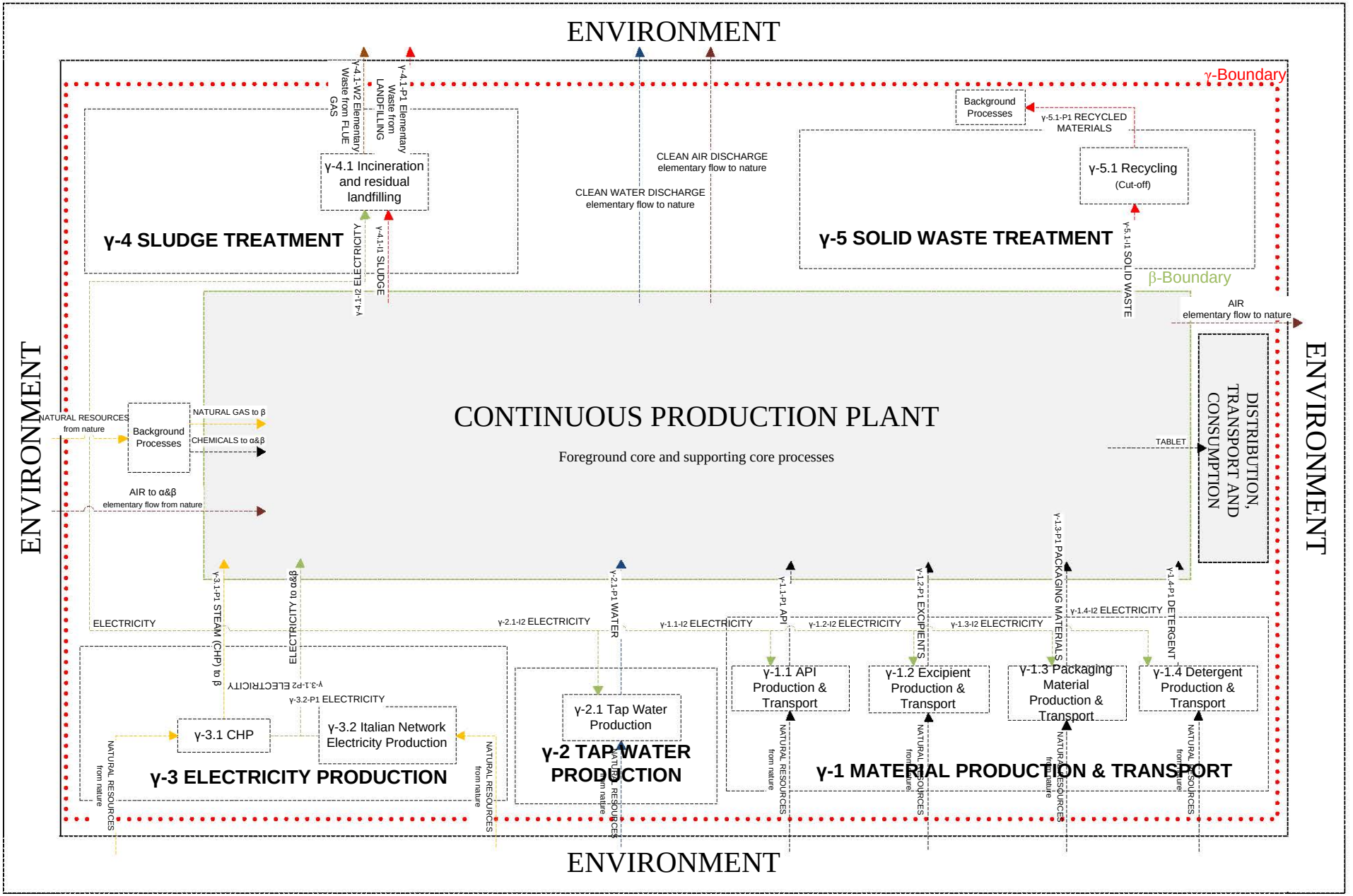
Annex A3.4: Continuous Flowchart TRAMACET® α system (related to Chapter 4)



Annex A3.5: Continuous Flowchart TRAMACET® β system (related to Chapter 4)



Annex A3.6: Continuous Flowchart TRAMACET® γ system (related to Chapter 4)



Annex A4: Resource efficiency TRAMACET® production (related to Chapter 4)

A4: Resource efficiency TRAMACET® production (related to Chapter 4)

Definition of three types of efficiencies. (1) simple efficiency; (2) rational efficiency; (3) utility efficiency.

EFFICIENCY	FORMULA
Simple efficiency (η1)	$\eta_1 = \frac{Ex_{pr} + Ex_w}{Ex_{in}}$
Rational efficiency (η2)	$\eta_2 = \frac{Ex_{pr}}{Ex_{in}}$
Utility efficiency (η3)	$\eta_3 = \frac{Ex_{pr} - Ex_{tr}}{Ex_{in} - Ex_{tr}}$

Summary of batch versus continuous wet granulation based tablet manufacturing resource efficiency analysis at process level (α level) (%).

	BATCH			CONTINUOUS		
PROCESS	**η_1**	**η_2**	**η_3**	**η_1**	**η_2**	**η_3**
α-1 DISPENSING	98.8	96.1	69.8	98.8	96.1	70.0
α-2 GRANULATION	69.7	60.3	23.8	94.3	85.2	61.3
α-3 MIXING	99.3	98.6	52.9	99.8	99.0	78.4
α-4 COMPRESSION	95.3	87.9	61.1	99.4	91.8	93.2
α-5 COATING	66.4	62.4	10.6	66.8	62.9	10.6
α-6 PACKAGING	98.7	97.8	41.9	98.7	97.8	42.2
TOTAL PROCESS LEVEL	78.6	71.7	24.4	86.5	79.9	32.8

Annex A4: Resource efficiency TRAMACET® production (related to Chapter 4)

Summary of batch versus continuous wet granulation based tablet manufacturing irreversibility generation and irreversibility reduction at process level (α level), FU = 1 tablet.

PROCESS	BATCH IRREVERSIBILITY (kJ/tablet)	CONTINUOUS IRREVERSIBILITY (kJ/tablet)	IRREVERSIBILITY REDUCTION (%)
α-1 DISPENSING	0.2	0.1	2.6
α-2 GRANULATION	6.1	0.8	86.6
α-3 MIXING	0.1	0.0	68.3
α-4 COMPRESSION	0.6	0.1	88.6
α-5 COATING	6.4	6.3	1.8
α-6 PACKAGING	0.6	0.6	1.8
TOTAL PROCESS LEVEL	14.0	8.0	43.1

A5: Stakeholder Survey (related to Chapter 6)

Annex A5: Stakeholder Survey (related to Chapter 6)

Global Sustainable Development in the Healthcare and Pharmaceutical Sector

A Stakeholder Survey Introduction

Project Introduction

Within the framework of sustainable development of pharmaceuticals in healthcare systems, there is an **emerging need towards streamlining and harmonization in terms of sustainability assessments of global supply mechanisms**.

As part of the **European Platform on Life Cycle Assessment (EPLCA)**, the **European Commission's Joint Research Centre (JRC**) kicked-off a project in 2015 on reviewing the state of the art of sustainability assessments used in pharmaceutical and healthcare systems. The three main objectives through **reviewing scientific literature**, gathering feedback through **surveys and expert interviews** are:

- **Reporting state of the art LCI and LCIA methods** used in pharmaceutical production and in evaluating environmental sustainability of current healthcare systems.

- **Evaluation of the possible construction of a so-called node in the Life Cycle Data Network (LCDN)** to enhance collaboration in (corporate) sustainability assessments; the construction of a Life Cycle Database for pharma + healthcare

- **Evaluation of the EC Production Environmental Footprinting (PEF)** method and identification of necessary requirements towards **Product Environmental Footprint Category Rules (PEFCR)**.

This Survey intends to gather expert opinions on above mentioned topics and the application of LCA in general on pharmaceutical products in healthcare pathways. For this, The Commission reaches out to a variety of stakeholders including private industrial companies, NGOs, researchers, policy makers, etc.

Confidentiality

Your answers will be processed and aggregated by the project team. All data obtained from participants will be kept confidential and will only be reported in an aggregate format (by reporting only combined results and never reporting individual ones). While we will not attribute specific comments to particular individuals or companies, we would like to show our appreciation for your input by acknowledging your participation as a stakeholder in the final report, if you approve.

Questions and feedback

If you have questions regarding the project, you may contact:

- Wouter De Soete at Wouter.DeSoete@UGent.be
- Simone Fazio at Simone.Fazio@jrc.ec.europa.eu
- Jo Dewulf at Jo.Dewulf@jrc.ec.europa.eu
- David Pennington at David.Pennington@jrc.ec.europa.eu
- Ingrida Hiunni at Ingrida.Hiunni@ec.europa.eu
- European Platform on Life Cycle Assessment
- Forum for Sustainability through Life Cycle Innovation

Annex A5: Stakeholder Survey (related to Chapter 6)

B Introductionary Questions

B.1 What is the name of your organisation?

B.2 What type of organization are you representing?

- ○ Private Organisation
- ○ Policy/Governmental (research) body/NGO
- ○ University/Research Institution
- ○ Sector or Trade Association/Consortium
- ○ Consumer (Hospital, Pharmacy, Patient, Doctors, etc.)
- ○ Other

B.3 Other:

B.4 What is your role in the organisation?

B.5 In which Member State or country are you based?

C Use of LCA

C.1 What are the main drivers for your organisation to perform Life Cycle Assessments (LCA)?

C.2 For what applications do you use LCA?

- ☐ Process optimisation (re-design)
- ☐ Sustainability reporting
- ☐ Product development
- ☐ B2B communication
- ☐ B2C communication
- ☐ Hotspot determination
- ☐ Other:

C.3 Other:

C.4 To assess the environmental sustainability of pharmaceutical products:

- ☐ A product group approach is sufficient
- ☐ A product-specific approach is favourable

C.5 What type of standards do you use to perform LCAs:

- ☐ None
- ☐ ISO
- ☐ ILCD
- ☐ WBCSD
- ☐ UK NHS Carbon Footprint Guidance
- ☐ Other:

C.6 Other:

C.7 What midpoint impact categories do you evaluate?

- ☐ Climate change (e.g. through Carbon Footprint indicator)
- ☐ Fossil fuel consumption
- ☐ Human toxicity
- ☐ Water consumption
- ☐ Other:

C.8 Other:

C.9 Do you evaluate endpoint categories? If so, which ones?

- ☐ Human Health (e.g. through DALY indicator)
- ☐ Ecosystem species (e.g. through species*year indicator)
- ☐ Natural resources (e.g. through surplus cost indicator)

C.10 To construct the Life Cycle Inventory (LCI), I use the following data sources:

- ☐ Bill of Materials
- ☐ MSDS files
- ☐ Batch Production Reports
- ☐ Equipment manuals
- ☐ Validation/Qualification Reports
- ☐ P&IDs
- ☐ Other:

C.11 Other:

C.12 What LCA approach is typically used in your organisation?

- ☐ Full-blown CtC or CtG LCA
- ☐ Streamlined LCA (e.g. focusing on Hotspots)
- ☐ Depends on the application (please explain):

C.13 Depends on the application:

D User experience and methodological challenges

D.1 What type of system boundaries are applied?

- ☐ Gate-to-Gate (GtG)
- ☐ Cradle-to-Gate (CtG)
- ☐ Cradle-to-Cradle (CtC)

D.2 If CtC, how do you assess pharmaceuticals or pharmaceutical metabolites in the environment (e. g. waste water)?

D.3 To your opinion, is there a need to expand system boundaries and take into account healthcare services related to a pharmaceutical product (e.g. doctor visits, hospitalisation, ...) and likewise shift Functional Units from physical atributes (e.g. 1 kg API, 1 tablet, ...) to the service offered to the patient (e.g. 1 year of treatment)

- ○ Yes
- ○ No
- ○ Depends

D.4 Please elaborate:

D.5 What do you perceive as the biggest hurdle in LCAs on Pharmaceuticals?

- B2B communications to obtain primary data from suppliers
- Lack of Life Cycle Data
- Confidentiality in data sharing
- Lack of integration of process design tools and LCA tools
- Lack of harmonisation of LCA methodologies in serving different markets

D.6 Do you think the lack of LCA data on chemical building blocks, solvents and pharmaceuticals is a crucial aspect that should be tackled?

- Yes
- No

D.7 If so, are you familiar with the Life Cycle Data Network (LCDN)?

- Yes
- No
- I have heard of it

Note: The Life Cycle Data Network (LCDN) was launched in Brussels on 6th February 2014 by Vladimir Sucha, Director General of DG JRC, and Alan Seatter, Deputy Director General of DG Environment. Through entry-level requirements, the Network allows for flexibility while facilitating the availability of coherent and quality assured life cycle data from different organisations. The Network is a non-centralised web-based infrastructure that ensures life cycle data can be easily accessed via searches, filtering, and sorting. The datasets in the Network come globally from any data developer /owner, e.g. industry, national LCA projects, research groups, and consultants.

More information on the Life Cycle Data Network: Click here
To browse datasets: Click here

Annex A5: Stakeholder Survey (related to Chapter 6)

D.8 To your opinion, could the establishment of an LCA database on pharmaceuticals and chemical building blocks (respecting confidentiality of data providers) be a preferred solution to overcome the issue of LCA data unavailability?

- Yes
- No

D.9 Do you think the lack of harmonisation of LCA methodologies in serving different markets is a crucial aspect that should be tackled?

- Yes
- No

D.10 If so, are you familiar with the Product Environmental Footprint method (PEF)?

- Yes
- No
- I have heard of it

Note: DG Environment has worked together with the European Commission's Joint Research Centre (JRC IES) and other European Commission services towards the development of a harmonised methodology for the calculation of the environmental footprint of products (including carbon).

This methodology has been developed building on the International Reference Life Cycle Data System (ILCD) Handbook as well as other existing methodological standards and guidance documents (ISO 14040-44, PAS 2050, BP X30, WRI/WBCSD GHG protocol, Sustainability Consortium, ISO 14025, Ecological Footprint, etc).

The final methodology was published as an Annex to the Commission Recommendation on the use of common methods to measure and communicate the life cycle environmental performance of products and organisations.

This version was developed taking into account the results of 2011 road test, the results of the invited expert consultation and of a consultation between Commission services.

Product Environmental Footprint Category Rules aim at providing detailed technical guidance on how to conduct a product environmental footprint study. PEFCRs complement general methodological guidance for environmental footprint by providing further specification at the product level. PEFCRs will increase reproducibility and consistency in product environmental footprint studies.

For more information: Click here

D.11 To your opinion, could the establishment of a Product Environmental Footprint Category Rule for pharmaceutical products be a preferred solution to come to a harmonised LCA methodology? If not, where do you see bottlenecks or what key aspects should be present in a harmonised method for LCAs on pharmaceutical products?

- ○ Yes
- ○ No

D.12 If not, where do you see bottlenecks or what key aspects should be present in a harmonised method for LCAs on pharmaceutical products?

A6: Multiple Regression Models (related to Chapter 8)

Correlation models of cumulative resource consumption at overall industrial level (γ) in terms of Cumulative Exergy Extraction from the Natural Environment (CEENE)

γ_A

$$LOG(CEENE_A) = 3.575 + 0.269 * LOG(Organic\ Solvent) - 0.693 * LOG(Molar\ Efficiency) + 0.550 * LOG(\Delta t) - 0.201 * LOG(\Delta T) - 0.043 * LOG(\#\ Reactors)$$

γ_B

$$LOG(CEENE_B) = 3.766 + 0.264 * LOG(Organic\ Solvent) - 0.685 * LOG(Molar\ Efficiency) + 0.518 * LOG(\Delta t) - 0.198 * LOG(\Delta T)$$

Annex A6: Multiple Regression Models (related to Chapter 8)

γ_C

$$LOG(CEENE_C) = 4.280 + 0.266 * LOG(Organic\ Solvent) - 0.709 * LOG(Molar\ Efficiency) + 0.328 * LOG(\Delta t)$$

γ_D

$$LOG(CEENE_D) = 4.946 + 0.543 * LOG(Organic\ Solvent) - 0.770 * LOG(Molar\ Efficiency)$$

γ_E

$$LOG(CEENE_E) = 5.032 + 0.648 * LOG(Organic\ Solvent)$$

A7: Calculating and Reporting Greenhouse Gas Emissions for Pharmaceutical Products (related to Chapter 8)

Annex A6: Multiple Regression Models (related to Chapter 8)

Public Health England

NHS England

Calculating and Reporting Greenhouse Gas Emissions for Pharmaceutical Products

This document describes a number of possible approaches to calculating the cradle to gate greenhouse gas (GHG) emissions from the manufacture of pharmaceuticals, with particular focus on small molecule pharmaceuticals in tablet form.

Organisations may wish to calculate the GHG emissions of pharmaceuticals to better understand and reduce these emissions over time. Additionally, the Sustainable Development Unit (SDU) is seeking from manufacturers more representative pharmaceutical specific GHG data to inform updates to the NHS Carbon Footprint and demonstrate success against the 10% GHG reduction target set for 2015. The most recent study can be found here: http://www.sduhealth.org.uk/documents/publications/HCS_Carbon_Footprint_v5_Jan_2014.pdf

Data submitted to the SDU to be incorporated into the NHS Carbon Footprint should preferably include cradle to gate and cradle to grave GHG emissions of the product (as supplied), per dose and per active ingredient.

When providing pharmaceutical data to the SDU it is preferred that the following hierarchy is used noting the approach taken, scope of what is included (eg cradle to gate, tablet and packaging, API only) and year that the manufacturing data represents.

Level 1. Specific appraisal of a pharmaceutical product using a recognised standard.
Level 2. Hybrid appraisal of a pharmaceutical product using specific API data and generic data for the remainder of the pharmaceutical (eg excipients, packaging, etc).
Level 3. Streamlined appraisal using a calculation for the API based on chemistry and generic data for the remainder of the pharmaceutical.
Level 4. Estimate of GHG emissions for a pharmaceutical product using generic categorisation.

Level 1: Specific GHG Appraisal of a Pharmaceutical Product

The preferred approach is for organisations to conduct a cradle to gate/grave GHG appraisal of a pharmaceutical using product specific manufacturing data. Relevant standards should be applied when conducting the GHG appraisal in order of preference:

a) Use the GHG Sector Guidance for Pharmaceuticals and Medical Devices.
b) Use a non-sector specific GHG standard such as GHG Protocol Product Standard, PAS 2050 or ISO 14067.

Note that this approach can be taken for all pharmaceuticals, not just for small molecule pharmaceuticals in tablet form. The level of accuracy of a study employing this approach is considered to be high.

Level 2: Hybrid GHG Appraisal of a Pharmaceutical Product (Using API Specific Data)

If a specific study of a pharmaceutical product cannot be completed the next level of appraisal involves using active pharmaceutical ingredient (API) specific manufacturing data and combining these data with estimates for other manufacturing data (eg excipients, packaging, etc). The following steps can be taken:

a) Collect specific API manufacturing data and calculate GHG emissions using the guiding principles in a recognised standard.
b) If the API is not manufactured by the pharmaceutical product supplier, ask the API manufacturer whether they have calculated GHG emissions of the specific API (typically expressed in kg CO_2e / kg of API).

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c) If data are available and the pharmaceutical is in tablet form then include the API value into the ABPI carbon footprint tool.
d) If data are available and the pharmaceutical is not in tablet form then report only the GHG emissions of the API, noting the difference in scope.

Level 3: Streamlined GHG Appraisal of a Pharmaceutical Product (Using API Chemistry)

If GHG data for API manufacture are not available from the supplier this can be estimated by collecting data for three key manufacturing variables based on API chemistry. The following steps can be taken:

a) Collect information on quantity of organic solvents, molar efficiency and duration of synthesis steps used in API manufacture and apply the approach in the article titled "Environmental Sustainability Assessments of Pharmaceuticals: An Emerging Need for Simplification in Life Cycle Assessments" to calculate the API GHG emissions.

- The formula to calculate GHG emission for a single synthesis step is: $LOG(CF_{Synthesis\ Step}) = -0.32 + 0.258 * LOG(Organic\ Solvent) - 0.907 * LOG(Molar\ Efficiency) + 0.33 * LOG(\Delta t)$
- The GHG emissions of the API can then be calculated by adding together the GHG emissions of each synthesis step multiplied by a conversion factor based on how much of the synthesis step output is required to produce the final API:
  $CF_{API} = \sum_{i=1}^{n} Conversion\ factor_{(i)} * CF_{Synthesis\ step(i)}$
- Where: $n =$ Number of synthesis steps
  $CF_{API} =$ Carbon footprint (GHG emissions) from API production (kg CO_2e / mol)
  $Converion\ factor = \frac{\text{Input moles of synthesis step required to produce API}}{\text{Output moles of final API}}$ (mol/mol)
  $CF_{\text{Synthesis Step}} =$ Carbon footprint from production of a synthesis step (kg CO_2e / mol)
  $Organic\ Solvent =$ Total net consumption of organic solvents in a synthesis step (L/mol)
  $Molar\ Efficiency = \frac{\text{Output moles of product from a synthesis step}}{\text{Input moles of product of raw materials in a synthesis step}}$ (mol/mol)
  $\Delta t =$ Time duration of a synthesis step per mole output (s/mol)

b) If the pharmaceutical is in tablet form then include the API value into the ABPI carbon footprint tool.
c) If data are available and the pharmaceutical is not in tablet form then report only the GHG emissions of the API, noting the difference in scope.

Level 4: GHG Estimate of a Pharmaceutical Product

If specific API data cannot be provided nor calculated then estimates may be used that are available in the ABPI tool using the following approach:

a) For small molecule pharmaceuticals in tablet form, use the ABPI carbon footprint tool and select the most appropriate estimate of API manufacture (either by entering chirality and number of synthesis steps or choosing a low, average or high estimate).
b) For other pharmaceuticals calculate a GHG estimate using other approach, noting the method employed.

Useful References

- GHG Sector Guidance for Pharmaceuticals and Medical Devices: http://www.ghgprotocol.org/feature/pharmaceutical-and-medical-device-sector-guidance-product-life-cycle-accounting.
- Environmental Sustainability Assessments of Pharmaceuticals: An Emerging Need for Simplification in Life Cycle Assessments: http://pubs.acs.org/doi/abs/10.1021/es502562d
- ABPI Blister Park Carbon Footprint Tool: http://www.abpi.org.uk/our-work/mandi/Pages/sustainability.aspx

Annex A6: Multiple Regression Models (related to Chapter 8)

Example Application of the Pharmaceutical GHG Formula

The formula presented in this document was developed by the research group EnVOC of the Department of Sustainable Organic Chemistry and Technology at Ghent University in collaboration with Janssen Pharmaceutica NV (2014).

Production data on 40 Active Pharmaceutical Ingredient (API) synthesis steps was used to determine the most relevant process parameters concerning the emission profile of a synthesis step. As an indicator for the performance of a synthesis step, the IPCC100a Carbon Footprint (CF) Life Cycle Impact Assessment (LCIA) method was used. A statistical backwards stepwise linear elimination procedure was applied on the primary parameters, with the correlated CF of the synthesis step as the response variable. A set of three parameters was determined which contained the largest predictive power: Organic Solvent Use (L/mole), Molar Efficiency (%), and Total Time Required (s/mole). The moles mentioned in the parameters are the intermediate or final products that result from a synthesis step. Using these parameters, a linear regression model was created. For a single synthesis step, the CF/mole can be calculated as in Equation 1:

$$LOG(CF) = -0.320 + 0.258 * LOG(Organic\ Solvent) - 0.907 * LOG(Molar\ Efficiency) + 0.330 * LOG(\Delta t) \quad (1)$$

For API production routes that contain more than one synthesis step, the yield of each synthesis step has to be taken into account. The yield is defined as the total moles of intermediate or final product obtained from the synthesis step divided by the theoretical maximum of moles obtainable from the synthesis step. The yield enables the calculation of a conversion factor for each synthesis step. As, due to the yield being less than 100%, proportionally more moles of intermediate from the first synthesis step will be required to produce 1 mole of end product.

For a hypothetical linear production route with three steps, the yields and conversion factors are as follows:

	Synthesis step A	Synthesis step B	Synthesis step C (final)
Yield	40%	60%	80%
CF (kg CO2-eq/mole)	3.0	9.0	7.5
Conversion factor	(1/0.8)/0.6 = 2.08	1/0.8 = 1.25	1

In order to calculate the total CF/mole product of a production route, the formula has to be applied as in Equation 2:

$$CF_{API} = CV_A * CF_A + CV_B * CF_B + CV_C * CF_C \quad (2)$$
$$CF_{API} = 2.08 * 3.0 + 1.25 * 9.0 + 1 * 7.5 = 25.0\ kg\ CO_2eq/mole\ API$$

With CF_{API} as the Carbon Footprint of the complete production route, CV_A as the conversion factor of synthesis step A and CF_A as the Carbon Footprint of synthesis step A. Parameters for synthesis steps B and C are analogue. Note that CF_A has undergone an inverse LOG transformation from the LOG(CF) that is the response variable from Equation 1.