K. Kümmerer
M. Hempel
(Eds.)

Green and

Green and Sustainable Pharmacy

Klaus Kümmerer · Maximilian Hempel
Editors

Green and Sustainable Pharmacy

Springer

Editors
Prof. Dr. Klaus Kümmerer
Department of Environmental
Health Sciences
University Medical Center Freiburg
Breisacherstraße 115b
79106 Freiburg
Germany
klaus.kuemmerer@uniklinik-freiburg.de
klaus@kuemmerers.de

Maximilian Hempel
Deutsche Bundesstiftung Umwelt
D-49090 Osnabrück
Germany
m.hempel@dbu.de

ISBN 978-3-642-05198-2 e-ISBN 978-3-642-05199-9
DOI 10.1007/978-3-642-05199-9
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2010924552

Cover Photo: Jim Barber - fotolia.com

Cover design: deblik, Berlin

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

Dear reader,

Pharmaceuticals are an indispensable part of our modern times, allowing for a high quality of life and an increased life expectancy. The last few years have shown that pharmaceuticals leave an partly unchanged impact on the environment after their use. As they are barely incompletely eliminated by sewage treatment, they are still found in relevant concentrations in the aquatic environment and drinking water. Human-toxicologically seen, the concentrations give no reason for concern, however, they are nevertheless a serious environmental problem. Furthermore, we know that the pharmaceutical production is connected with a high consumption of energy and resources and with the emergence of relatively large volumes of waste. All in all it appears that the production and use of pharmaceuticals can involve significant environmental impacts. Therefore it is only logical to pursue the question of how pharmacy and pharmaceutical industry can be more sustainable.

Which sustainable strategies can prevent the entry of pharmaceutical residues in environment and drinking water? How can we reduce resource consumption and waste in their production process? Is the concept of "Sustainable Chemistry" transferable to the pharmacy? How to reduce the entry of unused pharmaceuticals in the environment? What incentive options do we have to create a more sustainable pharmaceutical industry?

In order to find answers, a holistic approach is needed, identifying the environmental relief potential along the entire life cycle of pharmaceuticals.

The organizers of the "1st International Conference on Sustainable Pharmacy" attempted to discuss the aspects of the whole life cycle in one conference.

The result is very impressive: this book summarizes the current debate on sustainable pharmacy. The authors are from the pharmaceutical industry, environmental and social research, from regulatory agencies and banks. I thank the organizers of the "1st International Conference on Sustainable Pharmacy", the editors and authors for this readable work.

Deutsche Bundesstiftung Umwelt (DBU) Fritz Brickwedde

Preface and Scope of the Book

The presence of pharmaceuticals in the environment was first reported in the 1970s, but it wasn't until the advent of better analytical instruments that the topic began to gain more and more interest among scientists. It has attracted increased interest among the general public since the 1990s, when people began to become concerned about the presence of pharmaceuticals in their drinking water. Since then, pharmaceuticals in the environment have continued to be a "hot bed" of interest, as demonstrated by the huge number of publications on the topic (for an overview see the book "Pharmaceuticals in the Environment. Sources, fate effects and Risk", Springer Publisher). A broader view is now emerging covering the whole life-cycle of pharmaceuticals, the bodies responsible and people that decide on design, synthesis, manufacturing and use, as well as the introduction of pharmaceuticals into the environment: Green and sustainable pharmacy. This concept forms the background to this book. On the one hand, there are ongoing discussions about the different life stages of an active pharmaceutical ingredient and many publications on the subject have already appeared, research is in fact still in its infancy. On the other hand, the topic is complex, and activities focus on different scientific fields such as synthetic and medicinal chemistry, environmental hygiene, ethics, etc. Some issues are mainly being dealt with by industry (e.g. waste minimization), while others are part of a wide public discussion (genetically modified and patented organisms, the presence of pharmaceuticals in the environment). Some concerns have already lead to technological attempts to eliminate pharmaceutical residues in municipal waste water. We therefore felt that there was an urgent need to bring together the different groups of people involved, in order to connect the various issues raised and combine the many lines of discussion pursued in order to create a platform from which to move things forward in the interest of a more sustainable future.

These few thoughts may illustrate the challenges that green and sustainable pharmacy presents. This book endeavours to stimulate and encourage further discussion on green and sustainable pharmacy. Several issues have been addressed in contributions from different authors. Along the life cycle of a pharmaceutical this book contains five major parts:

- The first deals with general aspects such as pharmaceuticals in the environment, the links to green and sustainable chemistry, more general aspects of sustainable pharmacy and the possible role of pharmaceutical companies are addressed.
- The second part discusses the development, synthesis and production of pharmaceuticals. Only a few selected topics are highlighted here. Because synthesis-related issues are already covered by other publications, the authors were asked to address this issue on a more general level.
- The third part addresses the use and disposal of pharmaceuticals. The focus here is on the role of patients, doctors and pharmacists in contributing to green and sustainable pharmacy by proper use of the pharmaceuticals. An environmental classification system for pharmaceuticals as a valuable piece of information for doctors, pharmacists and patients is presented. We also take a look into the future: how will drug consumption develop?
- A classical topic is addressed in the fourth part, i.e. emission management, for which knowledge of the role of different sources such as hospitals and the general public is indispensable. A synopsis of effluent management strategies, i.e. effluent treatment, training and education as well as benign by design is given.
- In the fifth chapter, obstacles and incentives on the path to greener and more sustainable pharmacy are addressed. These span from legislative regulations and issues of patent life time to the possible role of banks and investors

This book does not claim to cover all the aspects of green and sustainable pharmacy. Rather, it attempts to provide an overview of the present state of knowledge based on different examples, typical lines of thought and the outcome of discussions on major issues. Since green and sustainable pharmacy is still in its infancy, it attempts to identify lack of knowledge and stimulate more activities on the way to sustainable pharmacy rather than to resolve ongoing discussions.

The book would not have been possible without the support received from our co-workers at the Applied Environmental Research Section of the Department of Environmental Health Sciences, University Medical Centre Freiburg, and the Deutsche Bundesstiftung Umwelt in Osnabrück, which gave us the time necessary to edit a book in such a new and demanding field. The idea for the book and its central theme arose at the 1st International Conference on Sustainable Pharmacy (http://www.dbu.de/ 550artikel27309_788.html) sponsored by the Deutsche Bundesstiftung Umwel, without which neither the conference nor the book would have been realised. Florian Keil and Hans-Christian Schaefer were both members of the team that planned and organized this conference on sustainable pharmacy. They contributed valuable discussions and raised important and interesting questions within the planning phase of the conference and the book. Thank you! Thank you also to all the authors who sacrificed their precious time to contribute to this book. Furthermore, we wish to thank all the participants of the conference for dedicating their time and knowledge, thus contributing to very open and productive discussions at the conference and fruitful contacts later on. Thanks to all of you for your contribution! Numerous discussions with colleagues, contributors to the book and other people have been stimulating. A big thanks to all those people who created

the opportunity for discussion, the open exchange of ideas and the sharing of results on green and sustainable pharmacy. This, as well as the encouraging comments and overwhelmingly positive feedback received after the conference encouraged the publisher and us to publish this book. Thank you to Christian Witschel and Marion Schneider and her team from Springer Verlag Heidelberg, who strongly supported the idea and helped make this book possible. Finally, a big thank you to our families, without whose patience and encouragement the book would not have been completed.

Freiburg, Germany — Klaus Kümmerer
Osnabrück — Maximilian Hempel
September 2009

Contents

Contributors

Monique van der Aa RIVM National Institute for Public Health and the Environment, 3720 BA Bilthoven, The Netherlands, Monique.van.der.Aa@rivm.nl

Simon W. Breeden Department of Chemistry, Green Chemistry Centre of Excellence, University of York, York YO10 5DD, UK, swb1@york.ac.uk

Staffan Castensson R&D Department, National Corporation of Swedish Pharmacies, Apoteket AB, SE-118 81 Stockholm, Sweden, staffan.castensson@apoteket.se

James H. Clark Department of Chemistry, Green Chemistry Centre of Excellence, University of York, York YO10 5DD, UK, jhc1@york.ac.uk

Christian G. Daughton Environmental Chemistry Branch, National Exposure Research Laboratory, U.S. Environmental Protection Agency, Las Vegas, NV 89119, USA, Daughton.Christian@epamail.epa.gov

Jutta Deffner Institute for Social-Ecological Research, D-60486 Frankfurt am Main, Germany, deffner@isoe.de

Thomas Dworak Ecologic Institute, A-1130 Vienna, Austria, thomas.dworak@ecologic.eu

Anders Ekedahl R&D Department, National Corporation of Swedish Pharmacies, SE-211 34 Malmö, Sweden, anders.ekedahl@apoteket.se

Konrad Götz Institute for Social-Ecological Research ISOE GmbH, D-60486 Frankfurt am Main, Germany, goetz@isoe.de

Bo Gunnarsson Apoteket AB, SE-118 81 Stockholm, Sweden, bo.gunnarsson@apoteket.se

Maximilian Hempel Deutsche Bundesstiftung Umwelt, D-49090 Osnabrück, Germany, m.hempel@dbu.de

Andreas Holzer Sustainability Analyst, Bank Sarasin & Co. Ltd, CH-4002 Basel, Switzerland, andreas.holzer@sarasin.ch

Eleftheria Kampa Ecologic Institute, D-10717 Berlin, Germany, eleftheria.kampa@ecologic.eu

Florian Keil Institute for Social-Ecological Research ISOE GmbH, D-60486 Frankfurt am Main, Germany, keil@isoe.de

Geertjan Kommer Centre for Public Health Forecasting, RIVM National Institute for Public Health and the Enviroment, 3720 BA Bilthoven, The Netherlands, geertjan.kommer@rivm.nl

Klaus Kümmerer Department of Environmental Health Sciences, University Medical Center Freiburg, Breisacherstraße 115b, D-79106 Freiburg, Germany, klaus.kuemmerer@uniklinik-freiburg.de

Cornelius Laaser Ecologic Institute, D-10717 Berlin, Germany, cornelius.laaser@ecologic.eu

Katherine H. Langford Norwegian Institute for Water Research (NIVA), NO-0349 Oslo, Norway, kla@niva.no

Michael Läufer LeadResource®, Global Human Resources Consultant, D-79111 Freiburg, Germany, mla@leadresource.de

Ludwig Metz D-93133 Burglengenfeld, Germany, m-family@gmx.de

Benoît Roig Department of Biodiagnostic and Metrology, LGEI Centre, F-30319 Alès, France, Benoit.Roig@mines-ales.fr

Ilene S. Ruhoy Basic and Clinical Sciences, College of Osteopathic Medicine, Touro University Nevada, Henderson, NV 89014, USA, Ilene.Ruhoy@tun.touro.edu

Hans-Christian Schaefer Deutsche Bundesstiftung Umwelt, D-49090 Osnabrück, Germany, hc.schaefer@dbu.de

Jürg Oliver Straub Corporate Safety, Health and Environmental Protection Department, F. Hoffmann-La Roche Ltd, CH-4070 Basle, Switzerland, juerg.straub@roche.com

Louise Summerton Department of Chemistry, Green Chemistry Centre of Excellence, University of York, Heslington, York, YO10 5DD, UK, ls25@york.ac.uk

John P. Sumpter Institute for the Environment, Brunel University, Middlesex UB8 3PH, UK, John.Sumpter@brunel.ac.uk

David Taylor WCA Environment Limited, Oxfordshire SN7 7YR, UK, david.taylor@wca-environment.com

Kevin V. Thomas Norwegian Institute for Water Research (NIVA), NO-0349 Oslo, Norway, kevin.thomas@niva.no

Evelyne Touraud LGEI Centre, F-30319 Alès, France, Evelyne.Touraud@mines-ales.fr

David J. Triggle School of Pharmacy and Pharmaceutical Sciences, State University of New York Buffalo, 14260 NY, USA; Graduate School of Education, State University of New York, Buffalo, 14260 NY, USA; The Center for Inquiry, Amherst, NY USA, triggle@buffalo.edu

Rodrigo Vidaurre Ecologic Institute, D-10717 Berlin, Germany, rodrigo.vidaurre@ecologic.eu

Gerald Vollmer European Environment Agency, 1050 Copenhagen, Denmark, gerald.vollmer@eea.europa.eu

Åke Wennmalm Stockholm County Council, S-104 22 Stockholm, Sweden, ake.wennmalm@sll.se

Part I
General Aspects

Chapter 1
Why Green and Sustainable Pharmacy?

Klaus Kümmerer

1.1 How It Began

First reports on the presence of pharmaceuticals in the environment were published in the early 1970s, but it was not until better analytical instruments became available that scientists began to develop a real interest in the topic. When in the 1990s concerns began to grow about the presence of pharmaceuticals in drinking water, the subject also aroused increased interest among the general public. Since then, pharmaceuticals in the environment have continued to be a "hot bed" of interest, as demonstrated by the huge number of publications (for an overview see the book "Pharmaceuticals in the Environment. Sources Fate Effects and Risk", Springer Publisher).

In the mid-1990s it became clear that focussing on end of the pipe treatment of environmental problems related to chemicals is not sustainable and will not be successful in the long run. It was learned that the main input was no longer the waste and exhaust resulting from the manufacture of chemicals. Instead, nowadays in developed countries at least the chemical products themselves cause the problems through their mere presence in the environment. Input sometimes happens on account of proper use. It was also learned that if this issue is to be tackled properly, solutions should not only be helpful for some few developed countries; rather a solution that works everywhere is needed. It was in this context that the concept of green chemistry was developed and began to gain momentum within chemistry (Anastas and Warner 1998, Clark and Smith 2005, Clark 2006, Lapkin and Constable 2009, http://en.wikipedia.org/wiki/Green_Chemistry_Metrics). Within this framework the focus is not only on the use or the synthesis of a chemical. Instead, the full life cycle of a chemical and its impact on the environment is looked at. This includes the raw materials used, synthesis, manufacturing, use and after-use life.

K. Kümmerer (✉)
Department of Environmental Health Sciences, University Medical Center Freiburg,
Breisacherstraße 115b, D-79106 Freiburg, Germany
e-mail: klaus.kuemmerer@uniklinik-freiburg.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_1,

The term "natural" is sometimes applied synonymously to mean harmless, green or even benign compounds. However, "natural" does not mean "harmless" or "green" or "sustainable" per se. Natural compounds are among the most toxic (botulinus toxin), and are persistent (e.g. minerals, wood and prions). If applied in high volumes in the wrong context they may also prove to be non-sustainable.

As for pharmaceuticals, it was learned in the 1990s that for synthesis of 1 kg of an active pharmaceutical compound, the amount of waste generated is up 50- to 100-fold the one generated within the synthesis of a bulk chemical (Sheldon 1992, 2007). This insight triggered activities within the pharmaceutical industries to reduce waste generation by different measures such as using different and more appropriate/"greener" solvents, or to develop synthesis routes using fewer less steps thus avoiding waste intensive purification steps. This was the eye opener for a broader view that brings the full life cycle of pharmaceutical products (Fig. 1.1) into focus, since it could be shown that such approaches can also save high amounts of money, thus rendering companies more competitive. As for pharmaceuticals in the environment, it has been learned that several techniques for the reduction of the input of pharmaceuticals into the environment are available (see Keil, Chap. 15, this book). However, it was found that each of these approaches has its specific shortcomings. Therefore, additional approaches such as people handling and using the compounds, i.e. doctors, pharmacists and patients. Another approach that focuses on

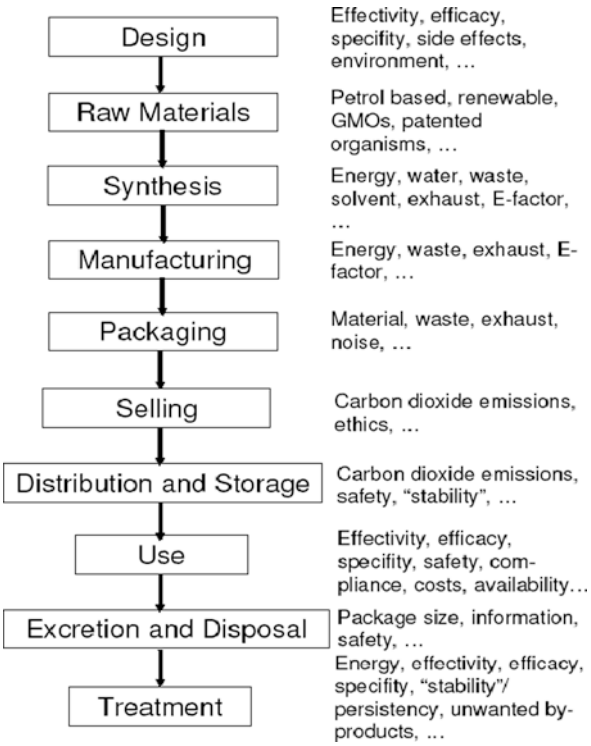


Fig. 1.1 The life cycle of a pharmaceutical and some points that are relevant for sustainability

the properties of the compounds came into focus – benign by design – the targeted design of a compound from its very beginning. These two strings of discussion can be connected by providing a broader view taking into account all environmental, social and economic issues. Along the life cycle of an API and an adjuvant, different issues are of importance with respect to sustainability. These are roughly depicted in Fig. 1.1.

1.2 Why Green and Sustainable Pharmacy?

Is green and sustainable not the same? Green pharmacy is the design of pharmaceutical products and processes that eliminate or reduce significantly the use and generation of hazardous substances and the prevention/reduction of environmental/safety and health impacts *at the source* (Clark 2006). For my understanding there are differences in the meaning of green and sustainable. "Green" often focusses on the chemical/pharmaceutical itself, including environmental aspects only. Sometimes safety and handling aspects are included.

For my understanding these are important points, however, they are not sufficient. For example, a new pharmaceutical can be green in terms of the quality and quantity of waste generated during its synthesis. Or renewable feedstock might have been used. However, the pharmaceutical may accumulate in the environment after excretion. If re-production of the renewable feedstock needs much water and fertilizer, is in competition with food production or depends on an endangered species it may not be called sustainable. The same holds, if the compound itself is "green" or even sustainable, however, the material flows connected to its production, distribution and usage are very large (in terms of quantity and/or in terms of quality) or depend on non-renewable resources (Hofmeister and Kümmerer 2009, Kümmerer and Hofmeister 2008). Another point is that greener products or chemicals may become less green or even problematic if they are produced and applied in high volumes. For example: A green packaging material contains an antimicrobial to preserve its content such as food from spoilage. This antimicrobial can contribute to resistance by being transferred to the food or by being set free into the environment after the usage of the packaging. Thus, a, packaging may be "green" but not sustainable. A sustainable view would also ask what the origin of the food is (local, regional or distant source) and how long we want vs. we need to store it. Educating people on how to handle and store food properly would be a much more sustainable approach to reducing food spoilage rather than increasing the risk of antibiotic resistance. Another example is the inclusion of an antimicrobial in high concentrations into bio-polymers only for the improvement of film structure. In terms of legislation, in such cases the antimicrobials are handled as simple chemicals. However, in fact they are antimicrobials that are used and spread uncontrolled with all the consequences of its use. Such a view is neither responsible nor sustainable. What will happen after the breakdown of the materials? Will the antibiotic be released into the food chain or the environment, contribute to resistance and will it eventually reach

drinking water? A similar question for drugs may be: Is a drug still sustainable if the active ingredient is a green one but the expedients that may have a bigger share in the total weight are not? What about expedients that have endocrine disrupting properties such as phthalates?

The examples demonstrate the need to keep the full life cycle in focus. This also includes other aspects, such as corporate social responsibility and ethical questions. For example, one may argue that we cannot afford sustainable pharmaceuticals because this would result in fewer active compounds reaching the market. Or is every pharmaceutical sustainable since it offers some benefit? However, a different view may be to ask how many people do not have access to suitable medication at all (see Triggle, Chap. 3, this book), e.g. for financial reasons. Another different view may be to ask why are there indications for which no or no new pharmaceuticals are available? What are the costs compared to the benefit? What are undesirable side effects?

Different aspects are of interest along the life cycle of pharmaceuticals (Fig. 1.1). The design of an API or an adjuvant determines to a certain degree the sustainability issues during the following life stages of the compound. Therefore, in a sustainable approach it is necessary to already have in mind these stages at the very beginning (see Daughton and Ruhoy, Chap. 6, this book).

This may also save money and shorten the time to market. Amongst others, in silico-tools (Ekins 2007) can be helpful here as well as green chemistry metrics. What we expect from an ideal, modern API includes:

- Effective and efficient
- Receptor specific
- Reduced/no unwanted effects
- Metabolized to harmless metabolites
- Fast and full degradability after use is part of functionality

As for the raw materials, petroleum-based ones will probably still be the most important source. Since the absolute amounts needed by pharmaceutical industries is much lower than by chemical industries and for fuel, the shortage after peak oil will probably not have a direct impact on the raw materials used by the pharmaceutical industries. However, rising energy costs should be expected due to the shortage of petrol-based energy generation. In the chemistry sector that basis of raw material will perhaps change raw material base. Instead of petrol, new platform molecules from renewable feedstock will gain importance (see Clarke et al. Chap. 4, this book). However, renewable feedstock will also go along with certain limitations and specifics that are not yet fully understood Another issue is the role and handling of patented organisms, which may in some cases be genetically modified organisms.

As for synthesis, big progress has already been made during the last decade. The use of proper solvents, micro-reactors, catalysts and biosynthesis, improvements in yield, and the progress made in separation and extraction steps has resulted in a tremendous reduction of the amount of waste generated during synthesis of an API. Since this goes hand in hand with big savings, the progress made towards realising

green and sustainable pharmacy has been the biggest at this life stage compared to others where discussions and changes in practice are still in their infancy.

As for manufacturing, related emissions into the environment are normally low in North America and Europe. However, nowadays pharmaceuticals, especially generics, are most commonly manufactured in Asia, South America and Africa. It has been found that in India and in China emissions related to drug manufacturing are very high (Thomas and Langford, Chap. 14, this book, Larsson et al. 2007, Li et al. 2008a, b) in effluents and are still found in water from wells used as drinking water. Another point of interest is the type and amount of packaging material used. For these materials, sustainability along the full life cycle is also necessary. Appropriate package size contributes to the minimization of the volume of outdated drugs. There are no exact and reliable data available on the share of unused but sold pharmaceuticals (Ruhoy and Daughton, this book, Götz and Deffner, Chap. 10, this book, Vollmer, Chap. 11, this book, Castensson and Ekedahl, Chap. 12, this book). Estimates range from 10 to 35%. Consumption will probably increase (see van der Aa and Kommer, Chap. 13, this book).

The main impact from selling pharmaceuticals that can be addressed by companies is to establish proper locations for production and a proper vehicle park (see Taylor, Chap. 7, this book). To minimize carbon dioxide emissions caused by these activities is part of corporate sustainability (see Läufer, Chap. 5, this book). The opportunities and especially the limitations of effluent treatment as an end of the pipe technology are becoming more and more clear (see Sumpter, Chap. 2, this book, http://www.start-project.de, Jones et al. 2007, Wenzel et al. 2008, Kümmerer 2008a). Therefore, other approaches are urgently needed.

This is on the one hand a better understanding of the role of involved people (patients, doctors and pharmacists, see Götz and Deffner, Chap. 10, this book). On the users' side, proper selection of APIs can contribute to input reduction (see Wennmalm and Gunnarsson, Chap. 16, this book).On the other hand, the design of the molecules has to be addressed. As for the molecules themselves, a design that incorporates all functionalities needed for the use and the molecule's life after use is desirable (see Kümmerer, Chap. 9, this book, Anastas 2008, Kümmerer 2007, Daughton 2003). A broader view would see undesirable presence of pharmaceuticals in the environment as part of pharmacovigilance, then called ecopharmacovigilance (Kümmerer and Velo 2006). This approach to the future can also open up new market opportunities in the mid and long term. To promote such an approach incentives are necessary. These could be direct financial incentives, e.g. by extending the patent life time for sustainable APIs or indirect ones such as legislation (see Holzer, Chap. 19, this book, Kampa et al., Chap. 17, this book, Roig and Touraud, Chap. 18, this book). There is an increase of innovation and economic advantages anticipated for healthy and environmental friendly products (German Advisory Board for Environment 2003). This may be an advantage for a pharmaceutical company that offers an APIs with properties comparable to others but with less environmental impact. Schering Plough announced an oral contraceptive containing estrogen estradiol (E2), which is similar to the one naturally present in a woman's body and nomegestrol

Table 1.1 Opportunities to reduce the input of pharmaceuticals into the environment (from Kümmerer 2008b, modified)

Who	Possible measures and activities
Pharmaceutical companies	Publication of data relevant for environmental assessment Publication of analytical methods and results Offering suitable package sizes Integration of environmental aspects into the development of new APIs and new therapies Dedication to green and sustainable pharmacy Fewer over-the-counter products Establishment of take back systems wherever not already present Establishment of corporate sustainability Research into sustainable pharmacy
Patients	Improvement of compliance Intake of APIs only if necessary and only after prescription by a medical doctor Out-dated drugs should not go down the drain; instead they should be returned to the pharmacy if a take back system is established, or into household waste if appropriate (check with local authorities and pharmacies) Proper hygiene
Pharmacists	Information of patients Participate in take back systems if appropriate (check with local authorities)
Hospitals	Integration of the delivering pharmacy/wholesaler into the handling of out-dated drugs Information of doctors and patients Proper hygiene
Medical doctors	Asking for appropriate package size Prescription according to environmental criteria if alternatives are available Information of patients
Health insurance	Requesting/paying for appropriate package size Keeping the necessary medical standards and demonstrating of reduction potential and economical benefits Information of doctors and patients
Veterinary medicine	Restrictive prescription Improvement of compliance Improvement of hygiene Less exchange of animals between flocks and farms Information of farmers
Waste water handling and treatment	Reduction of input by broken sewerage/piping Reduction of total water flow to be treated (separate piping of waste water and rain water) and thereby increasing concentration of APIs and efficiency

Table 1.1 (continued)

Who	Possible measures and activities
Drinking water treatment	Extended monitoring Advanced treatment if necessary Information of the general public
Authorities	Initiation and back up of communication between all stakeholders Development of limits/thresholds for APIs in different environmental compartments and drinking water
Banks	Inclusion of sustainability aspects into the rating of companies (manufacturers, retailers etc.)
Politics	Inclusion of APIs in environmental legislation More restrictive connection between environmental properties and authorization of pharmaceuticals Improvement of legislation for the management of out-dated drugs Incentives for greener and sustainable pharmaceuticals Promoting research and education in sustainable pharmacy

acetate, a hormone new in contraception, which resembles the progesterone a woman's body produces at certain times in her menstrual cycle and probably well biodegradable. The phase IIIa development program for NOMAC/E2 started in June 2006 (http://www.schering-plough.com/news/organon_news_article.aspx?url=/feeds/organon/OrganonNews/188519.xml&title=Pivotal%20phase%20IIIa%20trial%20for%20 Organon%E2%80%99s%20 novel%20 oral%20contraceptive,%20NOMAC/E2,%20complete%20recruitment). This new pill was probably not developed for ecological reasons (alone). However, this is another example demonstrating the feasibility.

The European Parliamernt and the European Comission already agreed in 2002 that within a generation chemicals should be produced and applied that do not have any impact on the environment (EU Parliament and EU-Commission 2002). This should also hold for pharmaceuticals. Table 1.1 summarizes the different stakeholders and their opportunities.

What is needed now is setting up a research agenda. Furthermore, an educational programme is necessary. To promote this programme and agenda success stories are needed. Some first examples are described in this book. However, many more are needed to promote green and sustainable pharmacy. At the same time, we need to learn more on the opportunities, challenges and limitations offered by green and sustainable pharmacy.

References

Anastas P (2008) Fusing green chemistry and green engineering: DesignBuild at the molecular level. Green Chem 10, 607

Anastas PT, Warner JC (1998) Green Chemistry: Theory and Practice. Oxford University Press, Oxford

Clark JH (2006) Green chemistry: Today (and tomorrow). Green Chem 8, 17–21
Clark JH, Smith P (2005) Basic principles of green chemistry. Innov Pharm Technol 16, 94–97
Daughton CG (2003) Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ Health Persp 111, 757–774
Ekins S (ed.) (2007) Computational Toxicology: Risk Assessment for Pharmaceutical and Environmental Chemicals. John Wiley and Sons, Hoboken
EU Parliament and EU-Commission (2002), Beschluss Nr. 1600/2002/EG des Europäischen Parlaments und des Rates vom 22. Juli 2002 über das sechste Umweltaktionsprogramm der Europäischen Gemeinschaft, 10.9.2002, Amtsblatt der Europäischen Gemeinschaften, L 242/1–15, 2002. 24
German Advisory Board for Environment (2003) Der Rat von Sachverständigen für Umweltfragen. Zur Wirtschaftsverträglichkeit der Reform der Europäischen Chemikalienpolitik. Stellungnahme Nr. 4, Juli, S. 29, Ziffer 38, 2003.
Hofmeister S, Kümmerer K (2009) Sustainability, substance flow management and time. Part II: Temporal impact assessment (TIA) as a new versatile tool for sustainable substance flow management. J Environ Manage 90, 1377–1384
Jones OH, Green PG, Voulvoulis N, Lester JN (2007) Questioning the excessive use of advanced treatment to remove organic micro-pollutants from waste water. Environ Sci Technol 41, 5085–5089
Kümmerer 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 Chem 9, 899–907
Kümmerer K (ed.) (2008a) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. 3rd edition, Springer Publisher, Berlin Heidelberg New York
Kümmerer K (2008b) Strategies for reducing the input of pharmaceuticals into the environment. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. 3rd edition, Springer Publisher, Berlin Heidelberg New York, 433–440
Kümmerer K, Hofmeister S (2008) Sustainability, substance flow management and time. Part I Temporal analysis of substance flows. J Environ Manage 88, 1333–1342
Kümmerer K, Velo GP (2006) Ecopharmacology: a new topic of importance in pharmacovigilance. Drug Safety 29, 371–373
Lapkin A, Constable D (2009) Green Chemistry Metrics: Measuring and Monitoring Sustainable Processes. Wiley, Chichester
Larsson DG, de Pedro C, Paxeus N (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Hazard Mater 148, 751–755
Li D, Yang M, Hu J, Ren L, Zhang Y, Chang H, Li K (2008a) Determination and fate of oxytetracycline and related compounds in oxyteracycline production wastewater and the receiving river. Environ Tox Chem 27, 80–86
Li D, Yang M, Hu J, Zhang Y, Chang H, Jin F (2008b) Determination of penicillin G and its degradation products in a penicillin production wastewater treatment plant and the receiving river. Water Res 42, 307–317
Sheldon RA (1992) Organic synthesis – past, present and future. Chem Ind-London, 903–906
Sheldon RA (2007) The E factor: fifteen years on. Green Chem 9, 1273–1283
Wenzel H, Larsen HF, Clauson-Kaas J, Høibye L, Jacobsen BN (2008) Weighing environmental advantages and disadvantages of advanced wastewater treatment of micro-pollutants using environmental life cycle assessment. Water Sci Technol 57, 27–32

Chapter 2
Pharmaceuticals in the Environment: Moving from a Problem to a Solution

John P. Sumpter

2.1 Introduction

Despite the fact that concern was raised a few decades ago about the (probable) presence of human pharmaceuticals in the aquatic environment (e.g. Aherne et al. 1985), the issue received little attention until two discoveries coincided. One was the finding by several analytical chemists, Thomas Ternes in particular, that many different human pharmaceuticals were present in effluents of sewage treatment works (STWs) (Ternes 1998). The other was the realisation that one particular human pharmaceutical, ethinyl estradiol (EE2), was contributing to the feminisation of male fish in effluent-dominated rivers (Jobling et al. 1998, Desbrow et al. 1998; reviewed in Sumpter and Johnson 2008). Together, these two discoveries raised a series of questions, of which the following are probably the most important:-

- How many different human pharmaceuticals are present in the aquatic environment?
- What are the concentrations of those pharmaceuticals in rivers?
- Which human pharmaceuticals adversely affect aquatic organisms, and what are those effects?
- What are the consequences, to individual organisms and to populations, of those effects?
- Do mixtures of pharmaceuticals cause effects that individual pharmaceuticals do not?
- Could pharmaceuticals interact with other chemicals present in the environment to cause unexpected effects.
- Are some pharmaceuticals partially degraded in the environment to "dead-end" transformation products, and do any of these cause effects?

J.P. Sumpter (✉)
Institute for the Environment, Brunel University, Middlesex UB8 3PH, UK
e-mail: John.Sumpter@brunel.ac.uk

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_2,

These questions were relatively obvious from the beginning, but answering them has not been straightforward. To date, more progress has been made on the chemical questions than the biological ones. These primarily scientific questions can be reconfigured into three problems, and it is these three problems that are the focus of this article. The three problems are:-

1. Many pharmaceuticals are present in the environment.
2. Some pharmaceuticals have been shown to have adverse effects on wildlife.
3. Drinking water may be contaminated with human pharmaceuticals.

I realise that some people, including well-informed people, may not consider these as "problems". Instead, they might consider them as issues meriting scientific research, the results of which might, or might not, demonstrate that they are problems. For example, if the research demonstrates that, although many pharmaceuticals are present in the aquatic environment, they do not pose any threat to aquatic organisms, nor to people drinking water derived from rivers containing human pharmaceuticals, then some would assert that there was no problem here. Others, though, would disagree, and would consider contamination of the environment by human pharmaceuticals (which are by definition biologically active chemicals) as undesirable, and not something that should be accepted. I will discuss each of these problems in turn, and present the evidence supporting each as a problem.

2.1.1 Problem 1: Many Pharmaceuticals Are Present in the Environment

There is now no doubt whatsoever that a large number of pharmaceuticals are present in the aquatic environment. So far, about 100 different pharmaceuticals have been detected in the aquatic environment, usually (and sometimes only) in STW effluents (Vanderford and Snyder 2006, Batt et al. 2008, Kasprzyk-Hordern et al. 2008). Those pharmaceuticals cover many different therapeutic classes, including analgesics, beta-blockers, selective serotonin reuptake inhibitors (SSRIs), fibrates, anti-epileptics, and steroids. This suggests that many pharmaceuticals are not completely removed during wastewater treatment at STWs.

In contrast to the considerable (and rapidly increasing) amount of information about the presence, and concentrations, of human pharmaceuticals in STW effluents, relatively little is known about the concentrations of human pharmaceuticals in rivers (although see Kasprzyk-Hordern et al. 2008). This is a very important data gap. Aquatic organisms do not live in STW effluents – they live in rivers. Hence, they are exposed to river concentrations of pharmaceuticals, not effluent concentrations. Due to dilution of STW effluent in rivers, concentrations of human pharmaceuticals in rivers will be lower than effluent concentrations. But by how much? Often effluent is diluted 10-fold, or more, upon entry into a river. Only if effluents are discharged

into small rivers, or even ditches, will the effluent not be appreciably diluted. These situations do, however, occur. Further, in very densely populated countries, with small rivers, many STWs discharge effluent into the same river, which could mean that chemical concentrations in rivers are higher than expected (see Williams et al. 2009, for a very comprehensive assessment of this situation with regard to steroid estrogens). Nevertheless, in general, river concentrations of human pharmaceuticals will be lower than effluent concentrations, and often very much lower. More information on river concentrations of human pharmaceuticals is much needed. It may well be that predicting concentrations, using modelling approaches, is a sensible way forward (see, for example, Johnson et al. 2008a, b).

Relatively little is known also about the fate and behaviour of human pharmaceuticals in rivers. Various processes might remove human pharmaceuticals from rivers. For example, the beta-blocker propranolol is very susceptible to photolysis (Liu and Williams 2007). Other pharmaceuticals might undergo biodegradation, which sometimes leads to the formation of recalcitrant products. Others might bind to particulate matter in the river. All these processes will lower the concentrations of pharmaceuticals in rivers. But by how much is largely unknown presently.

My personal view is that the presence of human pharmaceuticals in the environment is not, in itself, a problem. It is unsurprising, and only becomes of concern (a problem) if the pharmaceuticals cause effects on organisms that receive environmental exposure to them. However, although not necessarily a problem, I consider it undesirable that biologically active chemicals such as human pharmaceuticals enter the environment; it would be very much better if they did not, or if they do, that they are removed (e.g. degraded) very rapidly, before they have any opportunity to do harm. If they end up contaminating groundwater clean-up becomes extremely difficult, if not impossible.

2.1.2 Problem 2: Some Pharmaceuticals Have Been Shown to Have Adverse Effects on Wildlife

There are presently at least two examples of pharmaceuticals adversely affecting wildlife: EE2 and diclofenac. In the first case (EE2), the evidence is not yet conclusive, and the consequences of the effects are largely unknown. In contrast, in the second case (diclofenac), the evidence appears to be unarguable, and the effects have (very sadly) been dramatic. This example might well be the worst ever case of poisoning of wildlife by a chemical! These two examples are expanded on below.

2.1.2.1 Feminisation of Fish by EE2

EE2 probably plays a role in the feminisation of male fish that has been reported from many countries. Intersex fish (feminised males) were first found by accident, in settlement lagoons of two STWs in south-east England in 1976 (Sumpter and Johnson 2008). Comprehensive field surveys have shown that intersex fish

are widespread in British rivers (Jobling et al. 1998, 2006). They have also been reported from many other countries (see Tyler and Jobling 2008, for specific details). In most cases, these fish also had elevated plasma vitellogenin concentrations, suggesting exposure to one or more estrogenic chemicals. These feminised fish were associated with exposure to STW effluent, suggesting that estrogenic chemicals in effluents were the cause. A toxicity identification and evaluation (TIE) analysis of effluents indicated that steroid estrogens were the main estrogenic chemicals in effluents (Desbrow et al. 1998). Effluents were shown to contain a number of different steroid estrogens, both natural (e.g. estradiol) and synthetic (EE2), a result that has since been replicated many times, using effluents from many different countries. Thus, a human pharmaceutical, EE2, appears to play a role in the feminisation of male fish in many countries. It is less clear, however, whether EE2 does play a major role in this feminisation of fish, or perhaps even *the* major role, or alternatively whether it plays only a minor role, with natural steroids (such as estrone) playing the major role. Modelling studies suggest that EE2 plays a significant role (Sumpter et al. 2006), but this question is certainly not resolved.

A large number of laboratory studies, in which various aquatic species, especially fish, have been exposed under controlled conditions to known concentrations of EE2, have shown that some aquatic organisms are exquisitely sensitive to EE2 (reviewed in Caldwell et al. 2008). The predicted no effect concentration (PNEC) for fish is less than 1 ng/l, 1 ng/l causes some degree of feminisation, and concentrations as low as only 4 ng/l cause severe feminisation and prevent fish reproducing (e.g. Länge et al. 2001, Nash et al. 2004). There is thus no doubt that EE2 has the potential to cause dramatic effects on fish; other groups of organisms are less sensitive to it (Caldwell et al. 2008). What is mush less clear is exactly what concentrations of EE2 are present in rivers across the world, and hence what effects would be expected on fish as a consequence of those concentrations.

The consequence of the feminisation of wild fish is also unclear presently. Severe intersexuality has been associated with poor sperm quality and reduced fecundity (Jobling et al. 2002). However, even if a population of fish contains some severely intersex individuals (plus less severely affected fish, and some unaffected male fish), and these cannot reproduce, it is possible that the viability of the population will not be compromised. This is because it may not be necessary for all male fish in a population to be able to breed successfully for the population to be sustained long term. Thus, even if concentrations of EE2 in the aquatic environment (or at least some of it) are high enough to adversely affect a proportion of the fish, causing intersexuality, the population-level effects may be small, or even non-existent.

In summary, it is currently unclear whether or not the human pharmaceutical EE2 causes adverse effects on wildlife, though the weight of evidence suggests that it does, at least in some locations. The example of EE2 has undoubtedly highlighted the issue of human pharmaceuticals in the environment, and the study of it has revealed a great deal. However, it has also shown us that unless a human pharmaceutical causes acute effects on wildlife (as diclofenac has – see below), it may well be difficult to causally link a chronic adverse effect (occurring in wildlife) with a pharmaceutical, or group of similarity – acting pharmaceuticals.

2.1.2.2 Acute Poisoning of Oriental Vultures by Diclofenac

Although this example is one of veterinary, rather than human, use of a pharmaceutical, it nevertheless has a great deal to teach us all about the possible consequences of pharmaceuticals reaching the environment. This is currently the only well-documented instance of a pharmaceutical resulting in an adverse, population-level response in non-target, wild animals: in this case 3 species of Old World vultures (genus *Gyps*) in southeast Asia. The populations of all 3 species of vultures in this part of the world have crashed dramatically in the last decade. All 3 species have declined by 97%, or more (the exact number is unknown). The birds have been poisoned by diclofenac (Oaks et al. 2004), a non-steroidal anti-inflammatory drug (NSAID) used by veterinarians for the treatment of inflammation, pain, and fever in domestic livestock (especially cows). Vultures unintentionally ingested diclofenac when feeding on carcasses of livestock that had been treated with the drug shortly before their deaths (it is usually in this part of the world to leave the carcasses to be scavenged by vultures and other animals). Somewhere between 10 and 40 million vultures have been poisoned, and all 3 species are now critically endangered in the wild, and at very high risk of extinction. One of the 3 species, the oriental white-backed vulture (*Gyps bengalensis*) has gone from being probably the commonest large raptor in the world to being critically endangered in just 15 years. Probably to everyone's surprise, a pharmaceutical has been responsible for what is probably the worst case ever of accidental poisoning of any wild species of animal by any chemical!

Gyps vultures are extremely sensitive to diclofenac. The drug causes acute kidney failure, leading to large urate deposits on internal organs (visceral gout), and death, within a few days. The lethal does is of the order of 0.1–0.2 mg/kg (less than 1 mg per bird). Diclofenac concentrations in animal carcasses have been shown to be high enough to cause appreciable mortality if a vulture takes a single large meal from an animal that was given its last dose of the drug within a day or two of death (Green et al. 2006). Indian vultures from other genera are also in rapid decline (Cuthbert et al. 2006), although these declines have not, as yet, been causally linked to diclofenac. However, given that until very recently, some 5 million domestic animals were treated with diclofenac each year in India alone (Proffitt and Bagla 2004), it is not unreasonable to assume that those other species of vultures, and also other scavenging species of birds and mammals, ingested diclofenac in their food.

The extreme sensitivity of *Gyps* vultures to diclofenac has raised concerns that other species of vultures (including species in other genera) might also be as sensitive, and hence in considerable danger. Rapid death associated with visceral gout has been observed in two other vultures species (besides the 3 in southeast Asia), namely the African white-backed vulture, *Gyps africanus* and the Eurasian griffon vulture, *Gyps fulvus*, treated with diclofenac while in captivity (Swan et al. 2006). Hence, susceptibility to diclofenac poisoning appears to be widespread in the genus *Gyps*. Fortunately, New World Turkey vultures (*Cathartes aura*) appear to be at least 100 times less sensitive to diclofenac than do the Old World *Gyps* vultures (Rattner et al. 2008).

The utterly unexpected mass poisoning of Old World vultures by a NSAID has highlighted the lack of knowledge of the potential impacts of these drugs on scavenging birds. To determine the degree of threat to birds of accidental ingestion of diclofenac, Cuthbert et al. (2006) conducted a survey of veterinarians and zoos, enquiring about the use of NSAID to treat ill birds, and the outcomes of the treatment. They found that not only diclofenac, but also carprofen and flunixin, were associated with death. Other analgesics (e.g. ibuprofen) also cause mortality. NSAID toxicity occurred not only in raptors, but also in storks, cranes, and owls. This indicates that the potential impacts of the common worldwide use of NSAIDs to treat domestic animals may extend beyond *Gyps* vultures and could be significant (Cuthbert et al. 2006). One NSAID, however, namely meloxicam, has not been associated with any toxicity in birds; it has been administered to over 60 species without any obvious adverse effects (Cuthbert et al. 2007).

The catastrophic decline of vultures in southeast Asia due to diclofenac poisoning has highlighted many major deficiencies in our current knowledge concerning potential effects of pharmaceuticals on wildlife. Assuming that pharmaceuticals cannot reach the environment at concentrations that threaten wildlife has been shown to be wrong: they can. The route of exposure (domestic animals to scavenging birds) was not appreciated; it was very unexpected. The extreme sensitivity of *Gyps* vultures was also unknown and unexpected. These are just some of the lessons to come out this (very sad) example of mass poisoning of a large, very visual, bird by a pharmaceutical.

It is unclear presently whether these two examples (EE2 and diclofenac) will prove to be atypical – perhaps even the only examples of pharmaceuticals adversely affecting wildlife – or whether more, even many more, examples will be discovered. Laboratory experiments have suggested that low concentrations of some other pharmaceuticals can cause adverse effects on wildlife. For example, the beta-blocker propranolol has been reported to inhibit egg production in fish at low concentrations (Huggett et al. 2002). However, currently it is not known if this result will be repeatable, and/or whether propranolol concentrations in the aquatic environment can be high enough in certain locations to affect (inhibit) egg laying in wildlife.

2.1.3 Problem 3: Drinking Water May Be Contaminated with Human Pharmaceuticals

There are two aspects to this problem. One is whether there is, or is not, any public health issue due to the presence of human pharmaceuticals in the drinking water supply. The other is that, even if there is not a public health issue, people may not want pharmaceuticals in the water they drink: there may be a public perception issue to address.

The evidence that there are human pharmaceuticals in the drinking water supply (potable water) is not particularly strong presently. Some authors have reported being able to detect some human pharmaceuticals in potable water (e.g.

Vanderford and Snyder 2006; Mompelat et al. 2009). Given that at least some pharmaceuticals (e.g. carbamazepine) appear very resistant to degradation in STWs and the environment, and that rivers can serve as a major source of raw water (that is subsequently purified by various means), it would not be surprising if trace amounts of some human pharmaceuticals were present in potable water in some places. Concentrations are likely to be extremely low: perhaps on average a few nanograms per litre. These extremely low concentrations will prove an analytical challenge, and mean that it will probably be quite a few years before enough reliable data are available to enable the general situation to be known. Varying concentrations in the source water, and varying rates of removal during the treatment processes to produce potable water (because different processes are used in different places, and these vary in their efficiencies at removing micro-contaminants such as pharmaceuticals: Ternes et al. 2002, Radjenovic et al. 2008), will add further complications in determining the general situation.

Once the concentrations of pharmaceuticals in potable water are known, in theory it will be possible to conduct a risk assessment, to determine whether or not they pose any risk to health. It seems extremely unlikely that they will, primarily because the amount of any pharmaceutical in a litre or two of water (the amount likely to be drunk each day by an adult) will be very, very much smaller than the amount of that drug taken therapeutically by a patient. The difference could easily be a million-fold, or more. Even if people drank water contaminated with very low concentrations of pharmaceuticals throughout their entire life, the total amount of the most pharmaceuticals ingested may not reach the amount of a single therapeutic dose. For example, if a pharmaceutical was present in drinking water at a concentration of 20 ng/l, and a person drank 2 l of that contaminated water daily for 70 years, his/her lifetime intake would be 1 mg of that drug. Patients take much higher daily doses of many (though not all) drugs when they are being treated. Very preliminary attempts to estimate the potential risk posed by pharmaceuticals in the potable water supply have, unsurprisingly, reached that conclusion (Collier 2007; Johnson et al. 2008a). The fact that pharmaceuticals are not usually expected to do harm (they are intended to do good, of course) adds to the likelihood that their presence in drinking water is very unlikely to present a public health problem. However, people will almost certainly be exposed to mixtures of pharmaceuticals via drinking water, and the risk assessment of mixtures is in its infancy (Kortenkamp 2007). We need to be cautious of assuming that low-level exposure to multiple chemicals poses no risk (Kortenkamp et al. 2007). A precautionary approach may be sensible, even warranted.

Only one situation seems likely to result in a possible (and I emphasize the word possible) public health problem. That situation is exposure of the unborn child to toxic pharmaceuticals. This situation could arise if cytotoxic drugs, for example, were present in the drinking water drunk by a pregnant woman: her foetus/unborn baby may receive low level exposure to highly toxic drugs (drugs that are designed to kill dividing cells, for example). The examples of thalidomide and diethylstilbestrol (DES) serve as warnings that pregnant women can ingest pharmaceuticals (in these examples intentionally, of course) that can damage their unborn children, and should caution people in forming hasty opinions regarding safety.

Although it seems likely that the (potential) threat to the unborn child is of most concern, it is just possible that some other groups of people, particularly those in poor health, might be susceptible to the presence of pharmaceuticals in the water they drink. The elderly and infirm merit careful thought.

The second aspect of this problem is the public perception issue. It seems likely that people will not want pharmaceuticals in their drinking water (though I am unaware of any research that has directly explored the public's views). When the American media company Associated Press conducted an investigation on the presence of pharmaceuticals in the drinking water supply of Americans – and concluded that "a vast array of pharmaceuticals have been found in the drinking water supplies of at least 41 million Americans" – the story was extremely newsworthy, and received a great deal of interest, suggesting the public will be concerned. People may not want human pharmaceuticals in their drinking water, however low the concentrations are, and however insignificant the risk they constitute. People often do not make judgements in a manner considered rational by scientists.

2.2 Possible Solutions to the Problems Created by Pharmaceuticals in the Environment

2.2.1 Solution-1: Develop "Greener" Pharmaceuticals

To be effective (in patients), pharmaceuticals generally need to be relatively resistant to degradation. If they are to be taken orally (as most are), pharmaceuticals need to be able to survive the bacterial activity and acidic nature of the gastrointestinal tract. Once they have achieved this, and are absorbed, they travel in the hepatic portal vein to the liver, where many enzymes can de-activate chemicals. Effective pharmaceuticals have to survive these challenges, in order to reach their targets, and trigger their effects. Thus, pharmaceuticals need to be "tough", but this characteristic is undesirable once the pharmaceutical reach the environment, because it will prolong their existence in the environment. Thus, for example, fluorine is often incorporated into pharmaceuticals (Müller et al. 2007). "Block-buster" drugs such as prozac, lipitor and ciprobay contain fluorine. The carbon-fluorine bond is extremely strong, and hence makes the pharmaceuticals much more stable and resistant to degradation. This increases the bioavailability of the pharmaceutical: an asset in the patient, but a major disadvantage in the environment. So, "greener" pharmaceuticals probably should not contain fluorine (or other halogen) atoms. Pharmaceutical companies need to think about the environmental stability of a compound *early on* in the drug discovery process (i.e. 10 or more years before a successful drug reaches the market). Large pharmaceutical companies are now thinking along these lines (Lubick 2008). If new pharmaceuticals are structurally very resistant to degradation, they are likely to fail environmental risk assessments (now an obligatory component of registering any new pharmaceutical), which will probably limit sales of the drug.

2.2.2 Solution-2: Prevent Pharmaceuticals Reaching the Environment

A number of approaches are possible here. As covered earlier in this chapter, it is excretion of pharmaceuticals by people, in their urine and/or faeces, that primarily accounts for the presence of human pharmaceuticals in the aquatic environment of many countries. Redesigning toilets, so that urine does not enter the sewer system (as can be, and has been, done), would significantly reduce the amounts of human pharmaceuticals entering the sewerage system, and hence the aquatic environment (Borsuk et al. 2008).

Unused pharmaceuticals are often disposed of down a toilet (Bound and Voulvoulis 2005). This route whereby human pharmaceuticals enter the aquatic environment could fairly easily be substantially reduced if unused pharmaceuticals were returned to pharmacies, or collected in another way. Although it is unknown presently what percentage of drugs in the aquatic environment originates not from excretion by patients, but instead by disposal of unused drugs, and hence it is unclear what degree of reduction the collection of unused pharmaceuticals would have on concentrations of pharmaceuticals in the aquatic environment, nevertheless this step would probably be a relatively straightforward way of reducing the amount of drugs that reach the environment.

Neither of the approaches mentioned above would ameliorate the catastrophic "diclofenac and vultures" problem; both address only the issue of human drugs reaching the aquatic environment. Dealing with the emerging issue of veterinary drugs in the environment will not be easy. Livestock treated with veterinary drugs can, and do, excrete them into the environment. For example, intensively-reared livestock treated with steroidal growth promoting drugs (e.g. trenbolone) can excrete them into the aquatic environment, where concentrations can be high enough to masculinise wild fish (Orlando et al. 2004). Treated livestock that die, and are left in the environment to be consumed by scavengers, is a particularly difficult issue to address. Using non-toxic pharmaceuticals is the obvious initial approach (see above), but that relies on us knowing what pharmaceuticals are toxic to what animals, which we rarely do. The acute susceptibility of Old World vultures to diclofenac only serves to illustrate how difficult it will be to find "non-toxic" veterinary pharmaceuticals.

2.2.3 Solution-3: Improve the Efficiency of STWs

In developed countries (which are not the only countries using pharmaceuticals), nearly all wastewater passes through STWs before it is discharged to the aquatic environment. Wastewater treatment at STWs is already very effective at removing pharmaceuticals; concentrations of many are reduced by 90%, or more, in STWs (Ternes 1998, Batt et al. 2008). Some STWs appear to be significantly more effective than others at removing many micro-contaminants including pharmaceuticals.

However, it is often not clear why this is. A better understanding of how the pharmaceuticals are removed, especially in the activated sludge process (secondary treatment), would be very helpful. It may enable the activated sludge process to be optimized for removal of pharmaceuticals. Various types of tertiary treatment (e.g. addition of activated charcoal, ozonation, and chlorination) are also likely to reduce concentrations of pharmaceuticals in effluent. If it is inevitable that environmentally undesirable pharmaceuticals will get into the sewer system, then improving the efficiency of wastewater treatment in STWs is probably the only viable strategy to prevent these pharmaceuticals reaching the aquatic environment in concentrations high enough to do harm.

2.3 Conclusions

The presence of human and veterinary pharmaceuticals in the environment is a relative new issue. We still do not know the magnitude of the issue, nor the size of the problem. With the exception of diclofenac killing tens of millions of vultures, there is currently very little evidence that pharmaceuticals in the environment is a serious problem. However, that one exception is not only an extremely serious environmental problem, but it also illustrates only too vividly our lack of knowledge of the issue. We do not know which pharmaceuticals are reaching the environment, how they can get there (in the carcasses of dead livestock was a real surprise), which animals will receive exposure, and what the effects of that exposure will be (if any, of course). All these unknowns only serve to illustrate that "greener" pharmaceuticals are needed, so that the current problems caused by pharmaceuticals in the environment are minimized, or even prevented, before they have a chance to occur. It does not seem either sensible, or desirable, to me to have extremely biologically potent chemicals such as pharmaceuticals in the environment. It is probably inevitable that some will adversely affect some organisms. Many challenges lie ahead in the movement towards "greener" pharmacy, but these are not insurmountable, and need to be vigorously addressed.

References

Aherne GW, English J, Marks V (1985) The role of immunoassay in the analysis of microcontaminants in water samples. Ecotox Environ Safety 9, 79–83

Batt AL, Kostich MS, Lazorchak JM (2008) Analysis of ecologically relevant pharmaceuticals in wastewater and surface water using selective solid-phase extraction and UPLC-MS/MS. Anal Chem 80, 5021–5030

Benotti MJ, Trenholm RA, Vanderford BJ, Holady JC, Stanford BD, Snyder SA (2009) Pharmaceuticals and endocrine disrupting compounds in US drinking water. Environ Sci Technol DOI: 10.1021/es801845a

Borsuk ME, Maurer M, Lienert J, Larsen TA (2008) Charting a path for innovative toilet technology using multicriteria decision analysis. Environ Sci Technol 42, 1855–1862

Bound JP, Voulvoulis N (2005) Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environ Health Perspect 113, 1705–1711

Caldwell DJ, Mastrocco F, Hutchinson TH, Lange R, Heijerick D, Janssen C, Anderson PD, Sumpter JP (2008) Derivation of an aquatic predicted no-effect concentration for the synthetic hormone, 17α-ethinyl estradiol. Environ Sci Technol 42, 7046–7054

Collier AC (2007) Pharmaceutical contaminants in potable water: Potential concerns for pregnant women and children. EcoHealth 4, 164–171

Cuthbert R, Green RE, Ranade S, Saravanan SS, Pain DJ, Prakash V, Cunnigham AA (2006) Rapid population declines of Egyptian vulture *Neophron percnopterus* and red-headed vulture *Sarcogyps calvus* in India. Anim Conserv 9, 349–354

Cuthbert R, Parry-Jones J, Green RE, Pain DJ (2007) NSAIDs and scavenging birds: Potential impacts beyond Asia's critically endangered vultures. Biol Lett 3, 90–93

Desbrow C, Routledge EJ, Brighty GC, Sumpter JP, Waldock M (1998) Identification of estrogenic chemicals in STW effluent. I: Chemical fractionation and in vitro biological screening. Environ Sci Technol 32, 1549–1558

Green RE, Taggart MA, Das D, Pain DJ, Kumas CS, Cunnigham AA, Cuthbert R (2006) Collapse of Asian vulture populations: Risks of mortality from residues of the veterinary drug diclofenac in carcasses of treated cattle. J Appl Ecol 43, 949–956

Huggett DB, Brooks BW, Peterson B, Foran CM, Schlenk D (2002) Toxicity of select beta-adrenergic receptor-blocking pharmaceuticals (beta-blockers) on aquatic organisms. Arch Environ Contam Toxicol 43, 229–235

Jobling S, Coey S, Whitmore JG, Kime DE, Van Look KJW, McAllister BG, Beresford N, Henshaw AC, Brighty GC, Tyler CR, Sumpter JP (2002) Wild intersex roach (*Rutilus rutilus*) have reduced fertility. Biol Reprod 67, 515–524

Jobling S, Nolan M, Tyler CR, Brighty G, Sumpter JP (1998) Widespread sexual disruption in wild fish. Environ Sci Technol 32, 2498–2506

Jobling S, Williams R, Johnson A, Taylor A, Gross-Sorokin M, Nolan M, Tyler CR, van Aerle R, Santos EM, Brighty G (2006) Predicted exposures to steroid oestrogens in UK rivers correlate with widespread sexual disruption in wild roach populations. Environ Health Perspect 114(Suppl. 1), 32–39

Johnson AC, Ternes T, William RJ, Sumpter JP (2008b) Assessing the concentrations of polar organic microcontaminants from point sources in the aquatic environment: Measure or model?. Environ Sci Technol 42, 5390–5399

Johnson AC, Jurgens MD, Williams RJ, Kümerrer K, Kortenkamp A, Sumpter JP (2008a) Do cytotoxic chemotherapy drugs discharged into rivers pose a risk to the environment and human health? An overview and UK case study. J Hydrol 348, 167–175

Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ (2008) The occurrence of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs in surface waters in South Wales, UK. Water Res 42, 3498–3518.

Kortenkamp A (2007) Ten years of mixing cocktails: A review of combination effects of endocrine-disrupting chemicals. Environ Health Perspect 115(Suppl. 1), 98–105

Kortenkamp A, Faust M, Scholze M, Backhaus T (2007) Low-level exposure to multiple chemicals: Reason for human health concerns?. Environ Health Perpsect 115(Suppl. 1), 106–114

Länge R, Hutchinson TH, Croudace CP, Siegmund F, Schweinfurth H, Hampe P, Panter GH, Sumpter JP (2001) Effects of the synthetic oestrogen 17α-ethinylestradiol over the life-cycle of the fathead minnow (*Pimephales promelas*). Environ Toxicol Chem 20, 1216–1227

Liu Q-T, Williams HE (2007) Kinetics and degradation products for direct photolysis of β-blockers in water. Environ Sci Technol 41, 803–810

Lubick N (2008) Opening the "green pharmacy". Environ Sci Tehnol 42, 8620–8621

Mompelat S, Le Bot B, Thomas O (2009) Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water. Environ Int 35, 803–814

Müller K, Faeh C, Diederich F (2007) Flurine in pharmaceuticals: Looking beyond intuition. Science 317, 1881–1886

Nash JP, Kime DE, van der Ven LTM, Wester PW, Brion F, Maack G, Stahlschmidt-Allner P, Tyler CR (2004) Long-term exposure to environmental concentrations of the pharmaceutical

ethinyloestradiol cause reproductive failure in fish. Environ Health Perspect 112, 1725–1733

Oaks JL, Gilbert M, Virani MZ, Watson RT, Meteyer CU, Rideout BA, Shivaprasad HL, Ahmed S, Chaudhry MJI, Arshad M, Mahmood S, All A, Khan AA (2004) Diclofenac in residues as the cause of vulture population decline in Pakistan. Nature 427, 630–633

Orlando EF, Kolok AS, Binzcik GA, Gates JL, Horton MK, Lambright CS, Gary LE, Soto AM, Guillette LJ (2004) Endocrine-disrupting effects of cattle feedlot effluent on an aquatic sentinel species, the fathead minnow. Environ Health Perspect 112, 353–358

Proffitt F, Bagla P (2004) Circling in on a vulture killer. Science 306, 223

Radjenovic J, Petrovic M, Ventura F, Barcelo D (2008) Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment. Water Res 42, 3601–3610

Rattner BA, Whitehead MA, Gasper G, Meteyer CU, Link WA, Link WA, Taggart MA, Meharg AA, Pattee OH, Painn DJ (2008) Apparent tolerance of turkey vultures (*Cathartes aura*) to the non-steroidal anti-inflammatory drug diclofenac. Environ Toxicol Chem 27, 2341–2345

Sumpter JP, Johnson AC (2008) Reflections on endocrine disruption in the aquatic environment: From known knowns to unknown unknowns (and many things in between). J Environ Monit 10, 1476–1485

Sumpter JP, Johnson AC, Williams RJ, Kortenkamp A, Scholze M (2006) Modeling effects of mixtures of endocrine disrupting chemicals at the river catchment scale. Environ Sci Technol 40, 5478–5489

Swan GE, Cuthbert R, Quevedo M, Green RE, Pain DJ, Bartels P, Cunningham AA, Duncan N, Meharg AA, Oaks JL, Parry-Jones J, Shultz S, Taggart MA, Verdoorn G, Wolter K (2006) Toxicity of diclofenac to Gyps vultures. Biol Lett 2, 279–282

Ternes TA (1998) Occurrence of drugs in German sewage treatment plants and rivers. Water Res 32, 3245–3260

Ternes TA, Meisenheimer M, McDowell D, Sacher F, Brauch H-J, Haist-Gulde B, Preuss G, Wilme U, And Zulei-Seibert N (2002) Removal of pharmaceuticals during drinking water treatment. Environ Sci Technol 36, 3855–3863

Tyler CR, Jobling S (2008) Roach, sex, and gender-bending chemicals: The feminization of wild fish in English rivers. Bioscience 58, 1051–1059

Vanderford BJ, Snyder SA (2006) Analysis of pharmaceuticals in water by isotope dilution liquid chromatography/tandem mass spectrometry. Environ Sci Technol 40, 7312–7320

Williams RJ, Keller VDJ, Johnson AC, Young AR, Holmes MGR, Wells C, Gross-Sorokin M, Benstead R (2009) A national risk assessment for intersex in fish arising from steroid estrogens. Environ Toxicol Chem 28, 220–230

Chapter 3
Pharmaceuticals in Society

David J. Triggle

3.1 Introduction

The great discoveries in biology of the twentieth century have enormous potential to improve global health. There are, however, many challenges. How do we handle the fact that one billion people are overweight and obese while one billion are undernourished? That drugs for poor people are often considered to be a bad investment? Sick care or health care? Can health care be delivered effectively through a profit-driven "free market" system? What will be the role of pharmaceuticals in the twenty-first century? This role must be considered not only from a scientific perspective, but also from global social and economic perspectives.

> Now that the liability to, and danger of disease are to a large extent circumscribed – the effects of chemotherapeutics are directed as far as possible to fill up the gaps left in this ring (Paul Ehrlich 1913)

These words, written almost a century ago by Paul Ehrlich, a man often described as "The father of chemotherapy", now have an ironic ring to them written as they were on the eve of World War I and the beginning of mankind's most bloody century. Few, of course, will deny that the twentieth century realized major advances in health care and medicines delivery. From sulfonamides and antibiotics to vaccines and "smart" drugs tailored to specific gene mutations there has been in that murderous century huge progress in medicine and pharmaceutical delivery which, when coupled with advances in public health, have led to significant increases in human longevity and decreases in infant mortality.

D.J. Triggle (✉)
School of Pharmacy and Pharmaceutical Sciences, State University of New York, Buffalo, NY 14260, USA; Graduate School of Education, State University of New York, Buffalo, NY 14260, USA; The Center for Inquiry, Amherst, NY 14260, USA
e-mail: triggle@buffalo.edu

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_3,

3.1.1 Global Challenges Require Global Cooperation

Despite these advances we face new challenges in the twenty-first century from emerging diseases (AIDS, avian influenza), resurging old diseases (tuberculosis), from resistance to our antibiotic armory, from diseases generated by our life styles (obesity, diabetes, cardiovascular problems, etc.), from a progressively aging population with neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, etc) and from a biological "event" whether from a deliberate terrorist or Government self-inflicted act or a laboratory "accident". Today, both the "rich world" and the "poor world" suffer from unmet medical needs in access to and availability of pharmaceuticals, albeit for differing reasons (Schmid and Smith 2007).

Thus, the promise of Ehrlich's words remains significantly unfulfilled and the world faces challenges at this beginning of the twenty-first century that are far larger and far more important than in any previous century. Population growth, energy availability, global climate change and food supply all of which directly impact individual and global health are our four contemporary "Horsemen of the Apocalypse" and their world-wide assault will demand unprecedented levels of global cooperation. And this cooperation must take place in a world still significantly divided into rich and poor communities where almost half live without adequate education, food, water and sanitation and without significant access to health care and pharmaceuticals, while the rich world too frequently follows policies that ensure the continuation of this division, despite the spectacular advances in science and medicine following Ehrlich's words. Progress will not be possible until the cycle of "poor health driving poverty" is broken. This is unlikely to occur if the present Washington-driven model of laissez-faire, unregulated free market Darwinism continues. Indeed, some evidence suggests that International Monetary Fund (IMF) interventions in Russia and post-communist Europe are associated with significantly worsened TB incidence, prevalence and mortality (Stuckler, King and Basu 2008). Science and medicine have delivered for the rich world, but party and politics have blinded our eyes and have limited the participation of the poor world.

Thus, the role(s) of pharmaceuticals in society must be considered not merely from the perspective of the necessary and underpinning science and technology, but also from the multiple perspectives of public health, safety, affordability and health care costs and priorities.

3.2 Tomorrow's Pharmaceuticals: The Drug Discovery Process

The traditional, and until recently, an extremely successful route of drug discovery has been largely driven by observations of the biological activity of a natural product or synthetic substance on a physiological or pathological process and frequently in the absence of the known molecular target or detailed structural information about the target. Subsequent structural modification and biological testing led through a "one molecule at a time" process to the final therapeutic agent (Fig. 3.1). Much of

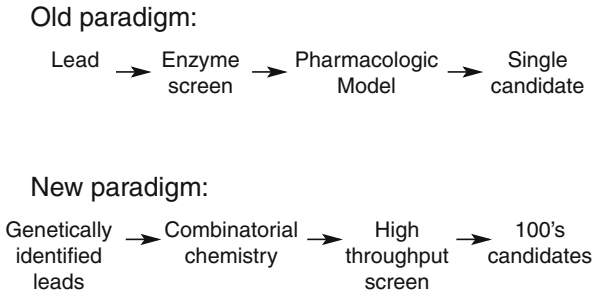


Fig. 3.1 A comparison of two paradigms of drug discovery

this discovery had its origin in bioactive natural products whose molecules have been "forged in the crucible of evolution" (Li and Vederas 2009). This process is now undergoing rapid change. The advent of genomics and the introduction of high throughput technologies for both chemical synthesis and biological screening have led to a new paradigm of drug discovery with target definition from gene interrogation initiating the process (Figs. 3.1 and 3.2). In turn this is leading to a revised paradigm for the pharmaceutical treatment of disease where an understanding of the molecular basis of the disease leads to a more appropriate choice of drug (Fig. 3.3). However, it is humbling to note that the discovery of a gene and genetic mutations associated with a disease does not lead automatically to either genetic or pharmaceutical cures. An excellent example is provided by cystic fibrosis where 20 years of discovery has led to much progress but no cure (Couzin-Frankel 2009).

A number of drugs currently clinically available, including cetuximab, imatinib, trastuzumab and gefitinib, owe their efficacy because they are directed against a subset of diseases caused by specific genetic mutations. It is likely that more efficacious pharmaceutical treatment of many other diseases will be accomplished through such pharmacogenetic profiling. Thus, hypertension remains, despite the availability of well over 100 drugs in multiple pharmacological classes, a very

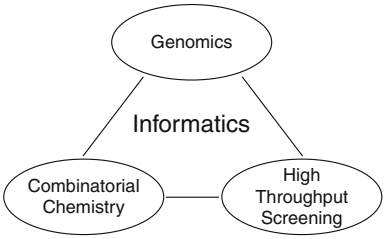


Fig. 3.2 Drug development in the twenty-first century. Targets are identified through gene reading and interrogation (genomics) and the high throughput techniques of combinatorial chemistry and in vitro screening are used to synthesize and examine millions of molecules. The resultant data are sorted through bioinformatics

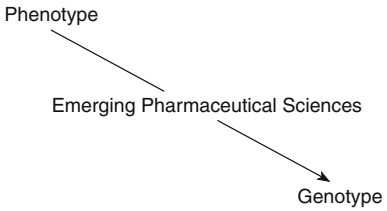


Fig. 3.3 The changing paradigm of therapeutic use in which diseases that treated by their phenotypic expression (fever, blood pressure numbers, tumor morphology etc) are now treated on the basis of their genotypic basis

poorly treated disease because, despite a common end-point of elevated blood pressure, it is of multifactorial origin and the matching of drug and patient remains largely an empirical trial and error process.

The technology of recombinant biology discovered in the latter part of the twentieth century has made possible the facile expression of human proteins such as insulin, human growth hormone, erythropoietin etc and the synthesis of new protein molecules, including humanized antibodies, for therapeutic use. These proteins can be expressed in plants and animals rather than in cultured cells, and in principle far more easily and cheaply. Thus human antithrombin is produced in goats and extracted from goat milk – "farmaceuticals" (Svoboda 2008).

3.2.1 Unrealized Potential

The presumed greater efficiency of the new drug discovery paradigm has, however, yet to be realized (Cuatrecasas 2006). There are several underlying reasons for this disappointment that underlie, at least in part, the declining rate of new drug discovery by pharmaceutical companies from the introduction of 53 new molecular entities in 1996 to only 17 in 2007 (Cuatrecasas 2006; for a review from the US perspective see General Accounting Office 2006).

First, the human genome is small – approximately 25,000 genes – far smaller than the approximately 150,000 genes originally predicted and of approximately the same size as the fruit fly. Hence, human biological complexity is determined not by a simple "one gene = one protein = one target" model, but rather by complex regulatory networks including multiple translation of the same gene, post-translational modification, epigenetic modification, multi-nodal cellular signaling networks and the newly emerging regulatory roles for small RNA sequences. Hence, the number of actual druggable targets is probably quite small, perhaps only a few hundred as opposed to the optimistically predicted hundred thousand or so.

Second, an excessively reductionist approach has been taken to the underlying biology of drug discovery. This focus at the isolated molecular level has led to the ignoring of the complex cellular signaling networks that define cellular and organ function. The failure to integrate this approach with considerations of systems

biology has led to "molecular success" – targets that are not validated and therapeutic failure (Williams 2004, Noble 2008, Hellerstein 2008).

Third, chemical space is huge, but biologically employed space (and hence exploitable space) is, at least in our universe, very small. For the typical small molecule drug there are some 10^{62} possible molecular structures and for the average size protein there are some 10^{390} possible amino acid arrangements!! Thus, it is clear that life as we know it on planet Earth has evolved to function within a very small area of chemically available space and it this very limited space that we must define and explore in the search for new pharmaceutical agents (Triggle 2009).

Fourth, it may be argued that the low-hanging and easily accessible fruit of the disease tree has been largely harvested over the past century and what remains are less tractable disorders, including the neurodegeneration of stroke, Alzheimer's and Parkinson's diseases and such disorders as autism etc.

Fifth, the dominant business model of the pharmaceutical industry has been the generation of "blockbuster" drugs with sales exceeding US$1 billion per year. Many smaller targets are thus ignored in this model and, in any event, emphasis is placed on the development of drugs for chronic rather than acute conditions since this ensures a constant market-generated demand. Hence, the discovery and development of new antibiotics has been neglected and with the development of resistance a major crisis in antibacterial therapy is unfolding (Roberts and Simpson 2008).

Sixth, and finally, this business model of drug development does not permit the development of drugs for those diseases for which the financial return is inadequate or even essentially non-existent. Thus, drugs for tropical diseases that largely affect the poor world are not a priority item for development in this business model (Butler 2007), and there has been an increased focus on "disease creation" for "life-style" drugs (Triggle 2006).

3.3 Tomorrow's Drug Development: Alternative Models

Whether a market-based system is the best approach to the delivery of health care and pharmaceuticals development and delivery is open to question. The United States practices a largely market-based approach with health care outcomes that are generally significantly inferior overall to those of the other member nations in the Organization for Economic Co-operation and Development (OECD) which enjoy a substantial amount of government participation and regulation (Commonwealth Fund 2007, 2008). The United States also has the highest overall cost of pharmaceuticals and the least equitable access to health care coupled with the highest percentage of children and adults living in poverty and the highest number and proportion of its population in jail amongst OECD members (Pew Charitable Trust 2008). The American model for health care delivery, or for that matter for the delivery of many other social services, is thus not one that should be copied although corporate influence worldwide may well attempt to ensure its dominance (Hegde 2005, Satrfield 2000). In fact, the combination of uncertainty of medical intervention and the highly asymmetric distribution of knowledge between the patient and the

health care industry makes a market-based system for health care both intolerable and immoral (Arrow 1963).

3.3.1 No Money, No Drugs?

The cost of pharmaceuticals is of particular significance in the poor world from two perspectives. First, the cost of existing drugs to treat diseases common to both the rich and poor worlds – AIDS, hypertension, respiratory diseases, cancer, etc – and where intellectual property rights are barriers to availability. Second, the question of drug development for diseases that are dominant in the poor world – malaria, schistosomiasis, leishmaniasis, sleeping sickness, etc – and for which there are few market incentives. Of the approximately 1,400 new drugs introduced in the 25 years prior to 2000 only 13 were for tropical diseases (Tucker and Makgoba 2008). This profound discrepancy in priority constitutes a "fatal imbalance" (Medecins sans Frontier 2001). In both instances the question to be posed is will the market-based discovery and regulatory processes for drug discovery and development currently in place suffice to generate adequate and affordable pharmaceutical care for the poor world? (Finkelstein and Temin 2008, European Commission for Competition 2009).

The current priorities for drug development can be measured from the public registry of interventional clinical trials now required as a condition for publication (De Angelis et al. 2004). Of the six largest therapeutic areas respiratory diseases, endocrinology and oncology showed increases over the period 2005–2007 (Karlberg 2008). Endocrinology was driven by increases in trials for obesity and diabetes and although infectious diseases had the fourth largest number of trials there was a decrease over this period with a particular decrease in the antibacterial area. Tropical and neglected diseases did not feature.

3.3.2 Supporting New Models

There is, in fact, in existence a variety of "alternative" structures and organizations that are directed at addressing both issues. Differential pricing by which the pharmaceutical company recovers only its marginal cost of drug production and compulsory licensing (the latter permitted with scarce enthusiasm by the World Trade Organization through TRIPs) are two approaches for the delivery of existing drugs to the poor world. Both approaches present difficulties because of the real possibility of back import of the drugs to the originating countries thus affecting the commercial pricing structure (Danzon 2007).

This approach is clearly not suitable for drugs for the tropical diseases that largely affect the poor world and alternative structures are necessary. It is perhaps worthy of note that as colonial powers European nations were interested in tropical diseases, for the non-altruistic reason that their own citizens were affected, in particular, their armies and their ruling bureaucracies. Climate change will increasingly move tropical disease patterns of occurrence to more temperate zones thus

increasing the motives for increased tropical disease research. A number of public-private partnerships exist for the development of new drugs for tropical diseases. These include, amongst others, Global Alliance for TB Drug Development, Malaria Medicines Venture, International AIDS Vaccine Initiative, Global HIV Vaccine Enterprise, Institute for One World Health, the Special Program for Research and Training in Tropical Diseases and financial support provided through, for example, the Wellcome Trust and the Bill and Melinda Gates Foundation (Butler 2007, Herrling 2006/2007) These cooperative ventures will need very significant and ongoing levels of financial support since there is little reason to doubt but that the cost of developing a new antimalarial or other tropical disease drug will be less than the cost for a new non-tropical disease drug currently estimated to be approximately (a disputed) $1 billion (DiMasi et al. 2003). Indeed, it is likely given the cost of new drug development that there will be more such cooperative arrangements in the future, including patent pooling or "open source" discovery (Srinivas 2006a, b). One such recently announced example is that between Merck, Pfizer and Lilly who will jointly develop new technologies through Enlight Biosciences.

3.4 Alternatives to Pharmaceuticals: The Role of Public Health

Although the trend in the rich world is to seek a "pill for every ill" and even for every imagined ill (Triggle 2006), it is important to note that individual and societal overall health is determined by multiple factors. These include access to and affordability of health care, public health infrastructure, and socio-economic status (relative poverty level) that contributes to "life-style".

Although medicine is often credited with the overall increase in societal health in the twentieth century there is abundant evidence to suggest that it is but one factor. A classic example of the role of public health measures is typified by Dr. John Snow of London who in 1854 stopped a cholera epidemic by the simple measure of removing the handle of a water pump that was supplying contaminated water to the inhabitants (Johnson 2006). Similarly, the incidence of respiratory tuberculosis in England and Wales had declined from 1840 by some 80% before antibiotics and vaccination were introduced (Hertzman 2001). Subsequent observations have amply confirmed the importance of public health measures including water, sanitation, vermin- and pest-free housing, abolition of toxic environments, and family planning services, as a vital underpinning to societal health (Sachs 2005). Absent such measures the availability of pharmaceuticals alone will, even if affordable, not suffice to create a healthy society.

3.4.1 Bad Habits as a Disease

Life style and environmental factors impact disease in a variety of increasingly well known ways and contribute to an expanding role for pharmaceutical intervention. Thus, tobacco use is associated with cardiovascular disease and lung cancer with

world-wide death rates of some 5 million per year, almost entirely preventable by the cessation of tobacco use (Brandt 2007). Yet considerable resource becomes allocated to the discovery and use of pharmaceuticals in the treatment of these tobacco-caused diseases. The role of diet in disease is significant, particularly with the increasing prevalence of adult and childhood obesity and the associated type II diabetes for which obesity is a major risk factor (Friedman 2000, Kopelman 2000, Taubes 2009). Although there are clearly multiple origins, including genetic components, there is little doubt but that life-style changes are major contributors to obesity and likely are mediated through so-called susceptibility genes that increase the risk of becoming obese under the appropriate environmental conditions (Kopelman 2000). Human history has not been marked until very recently with a systematic abundance of cheap, high energy and very palatable "fast food" (Schlosser 2001) the availability of which is facilitated by expansive and expensive marketing campaigns (Nestle 2006, Food, Inc. 2009). Its availability first in the Western world, but now increasingly in the expanding middle classes of China and India has, together with newly sedentary modes of human behavior, resulted in the present epidemic. We are thus faced with the irony of a world population with approximately 1 billion overweight and obese individuals and approximately the same number who are undernourished! This has created a large market for anti-diabetic and anti-obesity drugs and considerable emphasis is placed commercially on the development of these multi-billion dollar markets while the urgent need for public health measures is, by comparison, relatively neglected (Bray and Tartaglia 2000, Mello et al. 2006).

3.4.2 The Expanding Scope of Lifestyle Drugs

Similarly, there has been an expansion of pharmaceutical marketing efforts into the broad area of so-called "life style" pharmaceuticals and expanding the scope of existing diseases by broadening their definition (Angell 2004, Moynihan and Cassels 2005, Triggle 2006). Thus, disorders that are rare but with a pathological underpinning become, through expansive direct-to-consumer advertising, significant diseases for which expensive pharmaceutical remedies are available: such disorders include social anxiety disorder, irritable male syndrome, female sexual dysfunction, male impotence and "motivational deficiency disorder" – a phenomenon termed "disease-mongering" (Moynihan 2006, 2008, Triggle 2005a, b, 2006).

3.4.3 Wealth and Health

Finally, population health is determined by a number of factors including the overall wealth of the nation: generally population health increases, but in limiting fashion, with national wealth (for a discussion see Hertzman 2001). However, within individual populations health is affected by individual socio-economic status – increasing

income inequality being linked to decreasing health status (Farmer 1999, Wilkinson and Pickett 2006, Wilkinson 2000). Within these limits the more egalitarian societies have generally superior population health, presumably linked to a more even distribution of public health and related infrastructure.

3.5 The Road Ahead: Promises and Problems

Our previous century was one based on the great discoveries of physics made in the nineteenth and early twentieth centuries – clocks, steam engines, jet engines, typewriters, computers, etc. This century will be one based on the great discoveries in biology beginning with the reading of the human and other genomes (Judson 1979). Nowhere will this be more evident than in the practice of medicine. *Newborn children will start life with their genes already profiled, gene and protein microarrrays will make possible the delivery of "personalized drugs", gene and stem cell therapy will have come of age with major impact for degenerative disorders and injuries, and human cloning will be a reality. This new world will be one of artificial cells and cellular machines, many specifically created with an expanded genetic code and that will perform uniquely designated tasks, including the site- and disease-specific delivery of drugs and genes* (Triggle 2003). This promised future will, however, not arrive absent a set of potential problems including cost, access to the new medicines, ownership and safety. How will society address these problems and in what type of regulatory framework? There is no automatic and single set of answers to these challenges. And we should be careful in what we strive for: Huxley's "Brave New World" is surely not the direction that we wish to take (Huxley 1932: McKibben 2003).

Already most nations are facing serious challenges concerning cost and access to health care. With increasingly aging populations cost and demand for access to new medicines will increase. There are, in principle, two limiting solutions – a free-market model as essentially practiced in the United States where health care is rationed by ability to pay or the single-payer tax supported model of the United Kingdom where rationing is based on fund availability and cost-benefit analyses of pharmaceuticals (Callahan and Wasunna 2006). In practice, most nations run mixed models, and it is worth noting that their health outcomes are both superior (and less expensive) to those achieved in the United States (Commonwealth Fund 2008, Nolte and McKee 2008, Burd-Sharps et al. 2008).

3.5.1 Who Owns the Genes?

Three challenges in particular arise from the advent of biotechnology-derived medicines. First, the question of ownership of the intellectual property rights around the gene(s) of origin and, now the question of the conversion of these drugs into

generic form as their patents expire. Additionally, the use of these drugs (and others) will require knowledge of the patient's DNA sequence. Who will have access to this knowledge. The first question is encapsulated by a statement made by Jonas Salk who when asked who owned the new polio vaccine responded by saying, *Well the people I would say. There is no patent. Could you patent the sun?* (Smith 1990). This question remains a significant debating point with pharmaceutical and biotechnology companies arguing that gene patent ownership is critical to ensuring that the necessary financial and human investment takes place to ensure that new drugs do come to market and others arguing that such upstream patenting not only increases the costs of gene-based drugs and diagnostic procedures, but actually impedes research and development by creating a scientific "anti-commons" (Heller 2008, Heller and Eisenberg 1998, Srinivas 2006a, b, Triggle 2005b).

Related to this issue of ownership of DNA sequences of gene-derived biodrugs is the question of access to and use of patient DNA databases generated in the approach to pharmacogenetic based drug therapy. With countries, notably the United Kingdome and the United States, rapidly expanding their DNA databases questions of access to and use of loom large. In particular, will insurance companies and agencies access this information to seek reasons for exclusion or reduced coverage and will Government agencies access the information to seek individuals with "undesirable" traits. The eugenic road is a well traveled one (Brookes 2004).

3.5.2 New Safety Concerns

The conversion of protein drugs to generic form presents a particular challenge that does not exist with conventional small molecule drugs (Ledford 2007, Manheim et al. 2006, Wadman 2005.). Modifications, even minor, in the process of manufacture can produce differences in protein folding and post-translational modification that can affect biological properties (Walsh and Jefferis 2006). Given these issues questions arise as to whether a biogeneric drug (termed by some a "biosimilar" drug) will need to go through the same extensive clinical trials as the original molecule. The question remains unresolved (Grabowski 2008).

Issues of drug safety and regulation will loom larger with the introduction of new biodrugs. The public safety issues around the introduction and subsequent withdrawal of anti-inflammatory and anti-diabetic drugs and the restriction to use of antidepressants amongst others raises serious issues concerning the effectiveness of the regulatory agencies, notably the US Food and Drug administration, and the integrity of the clinical trial process itself. Some remedy is provided by the decision to have a public registry of all interventional clinical trials, but the question of whether drug trials should be publicly funded to avoid conflict of interest remains to be resolved (Baker 2008) and there are already extensive lobbying and litigation issues in place to slow or prevent the introduction of biogenerics (Pollack 2009).

A second issue of drug safety concerns environmental impact. Recent studies show that drinking water contains a vast array of pharmaceuticals – antidepressants,

steroid hormones, antibiotics, anticonvulsants, anti-inflammatories, etc – in drinking water (Dean 2007, Associated Press 2008). The levels are extremely low, far below clinically effective concentrations but these findings do raise the questions of the impact on both human and animal life of the constant exposure to low concentrations of biologically active agents. This issue must be considered in connection with the routine practices of adding antibiotics and hormones to animal feed in "industrial agriculture" that contribute both to antibiotic resistance and the contamination of ground water with bioactive materials. And also as part of a larger environmental issue for the introduction of endocrine disruptors from common plastic materials (Vandenberg et al. 2009, Gross 2007, Leranth et al. 2008).

The problem of environmental contamination will only become more serious with the introduction of new generations of biodrugs. Thus, the use of recombinant biology techniques for the production of bioactive materials in plants offers the more than theoretical possibility of horizontal gene transfer to other routinely consumed fruits and vegetables (Editorial Nature Biotechnology 2004, Adam 2009).

Acknowledgment This chapter was first published in, "A Health Future. Pharmaceuticals in a Sustainable Society", Published in collaboration between Apoteket AB, MistraPharma and the Stockholm City Council, Sweden. It is published here with some minor revisions and updates.

References

Adam D (2009) Down on the pharm. The Guardian, April 30. www.guardian.co.uk . Accessed July 24, 2009

Angell M (2004) The Truth About Drug Companies. Random House, New York

Associated Press (2008) Pharmawater. 1. March 9. http://nl.newsbank.com

Arrow KJ (1963) Uncertainty and the welfare economics of medical care. Am Econ Rev LIII, 941–973

Baker D (2008) Getting more for less. The not-so-obvious benefit of publicly funded trials for new drugs. The Milken Institute Review, Third Quarter, 46–53

Brandt AM (2007) The Cigarette Century. Perseus Books, New York

Bray GA, Tartaglia LA (2000) Medicinal strategies in the treatment of obesity. Nature 404, 672–677

Brookes M (2004) Extreme Measures. Bloomsbury Books, London

Burd-Sharps S, Lewis K, Martins EB (2008) The Measure of America. American Human Development Report, 2008–2009. Columbia University Press, New York

Butler D (2007) Neglected diseases. Nature 449, 157–182

Callahan D, Wasunna AA (2006) Medicine and the Market. Equity v. Choice. Johns Hopkins University Press, Baltimore, MD

Commonwealth Fund (2007) Mirror, mirror on the wall: An international update on the comparative performance of American health care. www.commonwealthfund.org

Commonwealth Fund (2008) Why not the best? Results from the national scorecard on U.S. health system performance, 2008. www.commonwealthfund.org

Couzin-Frankel J (2009) The promise of a cure: 20 years and counting. Science 324, 1504–1507

Cuatrecasas P (2006) Drug discovery in jeopardy. J Clin Invest 116, 2837–2842

Danzon PM (2007) At what price? Nature 449, 176–180

De Angelis C, et al. (2004) Clinical trial registration: A statement from the International Committee of Medical Journal Editors. N Engl J Med 352, 2436–2438

Dean C (2007) Drugs are in the water. Does it matter? New York Times, April 3. www.nytimes.com

DiMasi JA, Hansen RW, Grabowski HG (2003) J Health Econ 22, 151–185
Editorial Nature Biotechnology (2004) Drugs in crops – the unpalatable truth. Nat Biotechnol 22,~133
Ehrlich P (1959) Papers reprinted in the collected papers of Paul Ehrlich. In: Himmelweit F, Marquardt M, Dale HH (eds.) Chemotherapy 3. Pergamon Press, Press, London, pp. 505–518
European Commission for Competition EU competition inquiry into pharmaceutical sector. www.Ec.europa.eu/commission. Accessed July 27, 2009
Farmer P (1999) Infections and Inequalities. The Modern Plagues. California University Press, Berkeley, CA
Finkelstein S, Temin P (2008) Reasonable Rx: Solving the Drug Price Crisis. FT Press, London and New York
Food I (2009) www.foodincmovie.com. Accessed July 27, 2009
Friedman JM (2000) Obesity in the new millennium. Nature 404, 632–634
General Accounting Office (2006) New Drug Development. Science, business, regulatory, and intellectual property issues cited as hampering drug development efforts. GAO-07-49. www.gao.gov
Grabowski H (2008) Follow-on biologics: Data exclusivity and the balance between innovation and competition. Nat Rev Drug Discov 7, 479–488
Gross L (2007) The toxic origins of disease. PLoS Biol 5, e193
Hegde BM (2005) Modern medicine – A boon or a bane. Kuwait Med J 37, 235–237, December
Heller M (2008) Gridlock Economy. How Too Much Ownership Wrecks Markets, Stops Innovation and Costs Lives. Basic Books, New York
Heller M, Eisenberg RS (1998) Can patents deter innovation? The anti-commons in biomedical research. Science 280, 698–701
Hellerstein MK (2008) A critique of the molecular target-based drug discovery paradigm based on principles of metabolic control. Advantages of pathway-based drug discovery. Metab Eng 10, 1–9
Herrling P (2006/2007) Building innovative partnerships in neglected disease research. Drug Discov World, 22–25, Winter
Hertzman C (2001) Health and human society. Am Sci 89, 538–545
Johnson S (2006) The Ghost Map. Riverhead Books, New York
Huxley A (1932) Brave New World. Harper Row, New York
Judson H (1979) The Eighth Day of Creation: Makers of the Modern Revolution in Biology. Simon and Schuster, New York
Karlberg JPE (2008) Trends in disease focus of drug development. Nat Rev Drug Discov 7, 639–640
Kopelman PG (2000) Obesity as a medical problem. Nature 404, 635–643
Ledford H (2007) The same but different. Nature 449, 274–276
Leranth C, Hajszan T, Szigeti-Buck K, Bober J, MacLusky NJ (2008) Bisphenol a prevents the synaptogenic response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. Proc Natl Acad Sci USA 105, 14187–14191
Li JE-H, Vederas JC (2009) Drug discovery and natural products: End of an era or an endless frontier? Science 325, 161–165
Manheim BS, Jr, Ranahan P, Dow KJ (2006) "Follow-on biologics": Ensuring continued innovation in the biotechnology industry. Health Affairs 26, 394–404
McKibben B (2003) Enough. Staying human in an engineered age. Holt and Company, New York
Medecins sans Frontier (2001) Fatal Imbalance. The crisis in research and development for drugs for neglected diseases. www.access.med-msf.org, http://www.msf.org
Mello MM, Studdert DM, Brennan TA (2006) Obesity – the new frontier of public health law. N Engl J Med 354, 2601–2610
Moynihan R, Cassels A (2005) Selling Sickness. Nation Books, New York
Moynihan R (2006) Scientists find new disease: Motivational deficiency disorder. BMJ 332, 745
Moynihan R (2008) Disease mongering is now part of the global health debate. PLoS Med 5, 0684–0686

Nestle M (2006) Food marketing and childhood obesity – a matter of policy. N Engl J Med 354, 2527–2529
Noble D (2008) Claude Bernard, the first systems biologist, and the future of physiology. Exp Physiol 93, 16–26
Nolte E, McKee CM (2008) Measuring the health of nations: Updating an earlier analysis. Health Affairs 27, 58–71
Pew Charitable Trust (2008) One in 100: Behind bars in America 2008. www.pewtrusts.org
Pollack A (2009) Costly drugs known as biologics promote exclusivity debate. New York Times, July 22, 2009. www.nytimes.com. Accessed July 25, 2009
Roberts L, Simpson S (2008) Deadly defiance. A series of articles on drug resistance. Science 321, 355–369
Sachs JD (2005) The End of Poverty. Economic Possibilities for Our Time. Penguin Press, New York
Schlosser E (2001) Fast Food Nation. The Dark Side of the All-American Meal. Houghton Miflin, New York
Schmid EF, Smith DA (2007) Pharmaceutical R&D in the spotlight: Why is there still unmet medical need? Drug Discov Today 12, 998–1006
Smith JS (1990) Patenting the Sun. Polio and the Salk Vaccine. William Morrow, New York
Srinivas KR (2006a) TRIPS, access to medicines and developing nations. Towards an open source solution. Working paper no. 248. Indian Institute of management, Bangalore, India. www.policyinnovations.org/ideas/policy_library/data/01492-35 k
Srinivas KR (2006b) Intellectual property rights and biocommons: Open source and beyond. UNESCo. www.unesco.org
Satrfield B (2000) Is US health really the best in the world? JAMA 284, 483–485
Stuckler D, King LP, Basu S (2008) International monetary fund programs and tuberculosis outcomes in post-communist countries. PLoS Med 5, 1079–1090
Svoboda E (2008) Old McDonald had a Pharm. Salon, June 11. www.salon.com
Taubes G (2009) Prosperity's plague. Science 325, 256–260
Triggle DJ (2003) Medicines in the 21st Century. Drug Dev Res 59, 269–291
Triggle DJ (2005a) Vaccines, viagra and vioxx: Medicines, markets and money – when life-saving meets life-style. Drug Dev Res 64, 90–98
Triggle DJ (2005b) Patenting the sun: Enclosing the scientific commons and transforming the university – ethical concerns. Drug Dev Res 63, 139–149
Triggle DJ (2006) Treating desires not diseases: A pill for every ill and an ill for every pill? Drug Discov Today 12, 161–166
Triggle DJ (2009) The chemist as astronaut: Searching for biologically useful space in the chemical universe. Biochem Pharmacol 78, 217–223
Tucker TJ, Makgoba MW (2008) Public-private partnerships and scientific imperialism. Science 320, 1016–1017
Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM (2009) Bisphenol-A and the great divide: A review of controversies in the field of endocrine disruption. Endocrine Reviews 30, 75–95
Wadman M (2005) Path to approval proves rocky for copycat biodrugs. Nature 438, 154–155
Walsh G, Jefferis R (2006) Post-translational modifications in the context of therapeutic proteins. Nat Biotechnol 24, 1241–1252
Wilkinson RG (2000) Mind the Gap. Hierarchies, Health and Evolution. Yale University Press, New Haven
Wilkinson RG, Pickett KE (2006) Income inequality and population health: A review and explanation of the evidence. Social Sci Med 62, 1768–1784
Williams M (2004) A return to the fundamentals of drug discovery? Curr Opin Invest Drugs 5, 29–33

Chapter 4
Green(er) Pharmacy

James H. Clark, Simon W. Breeden, and Louise Summerton

4.1 Introduction

Although the issue of pharmaceuticals in the environment has been known for many years in some quarters, it has recently come to the attention of the general public in a much more substantive way. This has led to a growing body of research on environmental risk assessment and the environmental classification of drugs, as well as on the stewardship of drugs post-manufacturing (Kümmerer 2007, Kümmerer 2008). As with any chemical-containing article it is important that we understand, control, avoid or minimise the impact of the drugs entering the environment, and the deliberately high biological activity of active pharmaceutical ingredients (APIs) makes this especially important. There are many authoritative publications on the impact of pharmaceuticals on the environment post consumer use, and so these issues will not be addressed in any significant way in this chapter, but very little work has been carried out on determining the environmental impact of pharmaceuticals prior to administration to the patient.

It is important to realise that the environmental impact of pharmaceuticals is not limited to the phase after which they have entered the environment: drugs like all chemical entities are the products of resource-intensive and often wasteful manufacturing processes. Thus it is crucial for the industry, regulators and consumers to be aware of the environmental impact of pharmaceutical manufacturing as well as the impact post consumer (see Fig. 4.1).

For APIs the environmental impact of manufacture is especially high on a per kilo basis though the number of kilos required is significantly less than other industry sectors: typical processes are multi-step, can involve reagents and intermediates that are chemically hazardous and toxic and invariably generate large volumes of hazardous waste, the disposal of which is itself an environmental burden (e.g. incineration of aqueous waste streams made flammable by the addition of organic

J.H. Clark (✉)
Department of Chemistry, Green Chemistry Centre of Excellence, University of York, York YO10 5DD, UK
e-mail: jhc1@york.ac.uk

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_4,

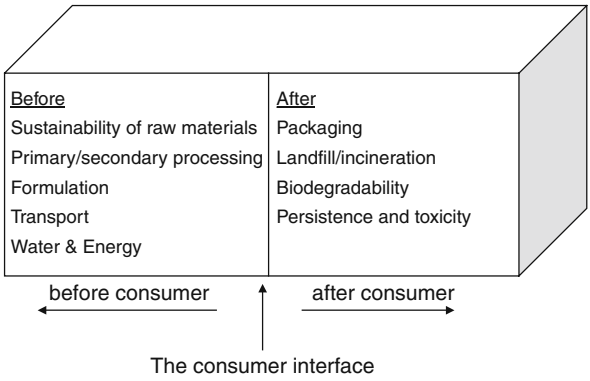


Fig. 4.1 Environmental impact of the lifecycle of a pharmaceutical

solvents). It is manufacturing processes such as these which encouraged the emergence of "green chemistry" in the 1990s when researchers and legislators joined forces to try to help chemical and related manufacturing companies make their processes safer, cleaner and more efficient (Anastas and Warner 1998).

Since that time there has been even more emphasis placed on environmental concerns, with increasing demands from all sections of society; regulators, industry itself, non-governmental organisations, and the general public for all the benefits of a modern day pharmacy but with a much reduced environmental impact. However,

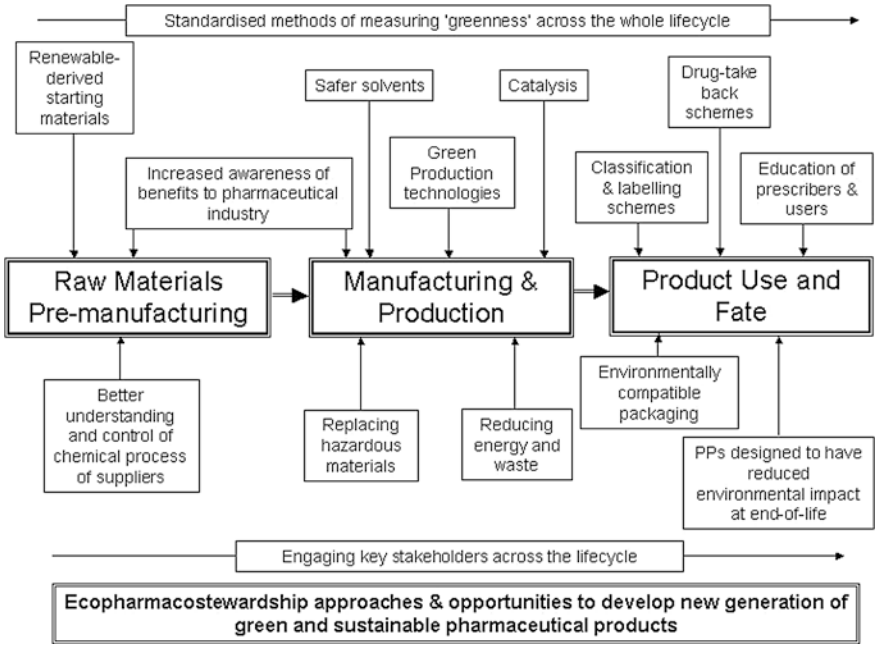


Fig. 4.2 Lifecycle issues of a pharmaceutical

as these demands are being made we are becoming ever more aware of the fact that a perceived environmental improvement in a product or process will have an effect on the life cycle of that product or process. In some cases a slight improvement in environmental impact in one area of the life cycle can result in a significantly increased environmental burden elsewhere. Thus it is important to have an awareness of the life cycle of a pharmaceutical and this is shown in Fig. 4.2.

This diagram shows where application of green chemistry principles can be used to assist in the development of green pharmacy. This diagram is a pictorial representation of the concepts that will be discussed in this chapter (headings in green) and within each of the sections we will explore the current state of the area and how the pharmaceutical industry, who are ultimately going to be the sector that will implement this change, is dealing with both the challenges and the opportunities.

4.2 What Is a Pharmaceutical?

Before we address the issues around green pharmacy it is important to answer a rather fundamental question: What do we mean when we refer to a pharmaceutical? Although instinctively this seems like a rather simplistic question, it is important that we understand exactly what we mean by a pharmaceutical as depending on this definition a number of differing strategies for minimisation of its pre-consumer environmental impact can be envisioned, although post consumer the differentials are much less. Furthermore depending on the type of pharmaceutical being considered the drivers for change, and the industry sector required to make that change, will be different.

Pharmaceuticals can be classified in a number of ways but for the purposes of considering the pre-consumer environmental impact of pharmaceuticals, and their associated drivers for change, the most appropriate method is to split the umbrella term, pharmaceuticals into three:

1. On Patent Prescription Only Pharmaceuticals

   Although this is what the general public has in mind when they hear the word, pharmaceutical, it is, by volume, the smallest sector, although by cost to health care providers it is the largest. The industry sector responsible for this class of pharmaceutical are the large research active pharmaceutical companies such as Pfizer, GlaxoSmithKline, AstraZeneca, Merck etc.

2. Off Patent Prescription Only Pharmaceuticals

   These class of pharmaceuticals are those that the research active pharmaceutical companies developed a number of years ago, but whose patent has expired, thus allowing generic manufacturers to produce the API. These generic manufacturers are not well known to the general public, nor indeed to many within the chemistry community, and despite efforts by the chemistry community, it has been unable to successfully engage with these companies.

3. Over The Counter Pharmaceuticals (OTCs)
   This class of pharmaceuticals is best represented by compounds such as aspirin, paracetamol, ibuprofen etc. and is probably not regarded as pharmaceuticals by the general public. The manufacturers of these pharmaceuticals are wide and varied and, similar to the generic manufacturers above, the pharmacy community has traditionally had trouble engaging with all players in this sector.

Where appropriate the different approaches required to achieve a green pharmacy for each of these class of pharmaceuticals will be highlighted, although it is hoped that the majority of what is discussed will be applicable across the board to ensure increased uptake of the approaches and thus maximum impact.

4.3 Standardised Methods of Measuring "Greenness" Across the Whole Lifecycle

Over the years there have been many approaches to try and define what is green and environmentally sound, with a number of measures such as E-factor (for the manufacture of APIs the E-factor is commonly 100+, in other words often less than 1% of the chemicals used to make the drug end up in the drug and with much of the rest being treated as waste), reaction mass efficiency, atom economy being proposed for chemistry reactions and processes (Sheldon 2007, Andraos 2005), and various environmental performance and sustainability indices, e.g. *life cycle assessment* available in a wider context. One of the major issues surrounding the green movement for many years was thus how do we measure green, and thus it was possible depending on ones own particular standpoint to argue whether A was greener than B, and furthermore this could often be backed up with statistics. However, recently there has been a gradual movement towards a universal measures of green-ness: Carbon Footprint.

Carbon footprint may not be the best metric for evaluating an environmental footprint, but it is at least being widely adopted by many industry sectors, and more crucially governments are now setting targets for companies, industry sectors, public sector organisations to achieve and failure to meet these targets will result in penalties being applied. It is also quite widely recognised by the general public.

Of particular relevance to the pharmaceutical industry in the UK, but with a potential global impact, is a recent carbon footprint report of the UK National Health Service (NHS).[1] This document shows that the NHS (in 2004, the latest date for which full data was available) has a carbon footprint of 18.6 $MtCO_2$ accounting for 25% of the entire public sector carbon footprint; a truly astonishing proportion, and far in excess of many countries throughout the world. Of this, procurement

[1] NHS SDU (2009) NHS England carbon emissions: carbon footprinting emissions projections to 2020 – January 2009, NHS Sustainable Development Unit, Cambridge.

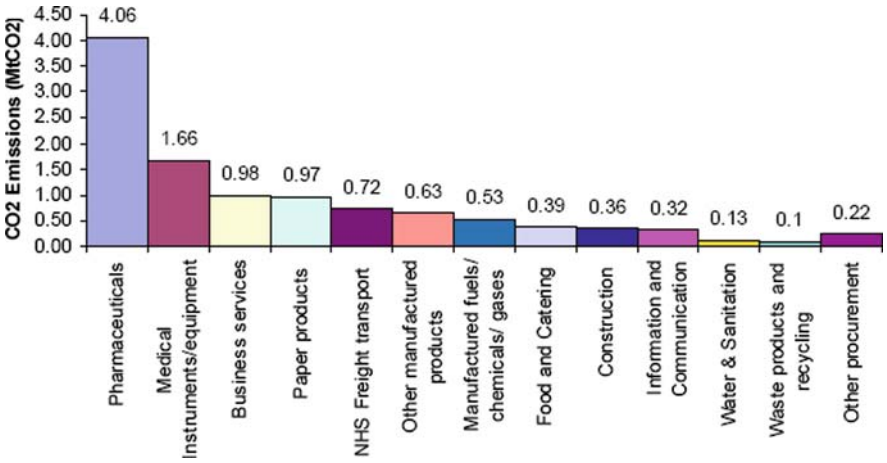


Fig. 4.3 Breakdown of NHS England 2004 procurement emissions (reproduced from Footnote 1)

accounts for 11.1 $MtCO_2$ (60%), building energy for 4.1 $MtCO_2$ (22%) and travel for 3.4 $MtCO_2$ (18%). Pharmaceuticals are by far the biggest contributor to the procurement carbon footprint as can be seen in Fig. 4.3.

Thus it can be seen that pharmaceutical procurement contributes approximately the same carbon footprint as the entire NHS energy requirements for heating, hot water, electricity consumption and cooling, and more than all travel undertaken on behalf of the NHS. This is largely incurred before the drugs reach their pharmacies and this is where the principles and practices of green chemistry can help to make a difference.

Accompanying this document was a summary of key actions[2]; three of which are below:

- The NHS should take every opportunity to manage its operations and procurement efficiently, thereby minimising wastage and carbon from the outset
- Further research will be undertaken into the carbon footprint of pharmaceuticals within the NHS to better understand this and to inform actions to produce significant reductions
- Local procurement, whole lifecycle costs and the environmental impact of financial decisions should be considered by all NHS organisations, in preparation for the use of carbon as a currency.

Whilst major suppliers to the NHS are currently facing awkward questions, in the longer term this is extremely encouraging, particularly to the research active pharmaceutical companies, who have spent many years developing their products

[2] NHS SDU (2009) NHS Carbon Reduction Strategy for England: Key actions, NHS Sustainable Development Unit, Cambridge.

and processes to be greener and now this can be used as a "currency" to gain a competitive advantage over the (possibly) less green generic manufacturers. This could also act as the customer pull required to make all manufacturers, including generics, make available their carbon footprint, and then to reduce it, to ensure market share is retained.

4.4 Raw Materials and Pre-manufacturing

It is generally accepted that the most effective way of making a product greener is to consider what steps need to be taken at the design phase to minimise adverse environmental impacts whilst at the same time maximising the benefit to society. Hence in order to develop greener pharmaceutical products it is essential that steps are taken to influence their development at an early stage in order to have the greatest impact.

4.4.1 Raw Materials

Obviously the starting point for any consideration of the environmental impact of a pharmaceutical will begin with the source of starting material. There are parallel approaches to the use of renewable resource derived starting materials: historically the pharmaceutical industry has taken its lead from nature with many of the (back-catalogue of) drugs on the market today originally being isolated from a natural source and then being improved, or modified in some way to mitigate any adverse, and increase the positive effects of the compound. Similarly many of the new pharmaceuticals coming on stream over the next number of years will be peptidic in nature and as such can be derived from a renewable resource.

This will only be for new drugs coming onto the market from the research active pharmaceutical companies; the vast majority of the ~3,000 drugs currently available are so called historic drugs, i.e. off patent prescription and OTCs, and furthermore although there is a drive for more bio-based drugs for the short and medium term the vast majority of new drugs will still be small molecule drugs. The majority of organic chemicals (>90%) in current use are derived from petroleum-based feedstocks. To be truly sustainable, many chemical industries (including pharmaceuticals) will require a shift towards the use of renewable feedstocks, through better utilisation of biomass (Clark and Smith 2005). It must also be borne in mind that the solution to sustainability is not that simple, renewable does not *necessarily* mean sustainable in that a full life cycle approach must be used to evaluate a supply chain with ideally full material and energy balances considered to ensure true sustainability.

Although the use of large and complex molecules derived from natural sources as a starting material for drug production (i.e. semi-synthesis) is current practice in the pharmaceutical industry, the use of biomass as a source of (small) platform molecules, from which a range of drugs can be derived, represents an area of green

chemistry that remains to be exploited by the pharmaceutical industry. Potential issues with this include:

- The price and availability of biomass derived platform molecules. Many biomass-derived chemicals identified as the future building blocks (Werpy and Peterson 2004) for the chemical industry are currently not commercially available and/or suffer both purity and cost issues. Extensive R&D efforts in green chemistry, biotechnology and engineering are therefore required to reduce processing and purification costs.
- The difficulty of the rapidly changing family of products made in the pharmaceutical industry. Nevertheless, some bio-derived platform molecules could directly replace existing petroleum-derived building blocks widely used by the pharmaceutical industry.
- A marked deficiency in the availability of high purity aromatics from renewable sources. The only significant source of aromatics in nature is lignin – an incredibly complex biopolymer, which represents an integral part of the cell walls of trees. Although lignin is cheap and widely available (by-product of pulp/paper and cellulosic ethanol production), new technologies remain to be developed to selectively convert this renewable resource into valuable aromatic fractions, which can be readily used as a starting material by the pharmaceutical industry.

Another emerging area within biomass-derived pharmaceuticals is biologics, which are considered by many as the future of medicine. Biologics are molecules produced in plant, animal or insect cells (e.g. antibodies, proteins) exhibiting high molecular complexity and generally providing more targeted treatment than traditional "small molecule" drugs. Once again, it must be emphasised that a full life cycle approach be considered for these molecules as well, to ensure that an improvement in the environmental credentials of the feedstock is not mitigated by harmful impact elsewhere in the supply chain. As more and more pharmaceutical companies commit to increase their biologics capability, new solvent extraction techniques that are less energy intensive and less hazardous will have to be developed to minimise their environmental impact.

4.4.2 Pre-manufacturing

4.4.2.1 Lead Identification

Scientists in lead identification have typically not been engaged in the move towards improving environmental performance and sustainability. Their role includes screening and testing compounds to find leading drug candidates for further development (Ng 2004). This provides a starting point for drug design and the lead compound(s) will not necessarily have the correct level of activity and may have undesired side effects (Patrick 2001).

A report on recent innovations and changes in the discovery process highlighted increasing pressures on managers in the discovery process to be more efficient in

identifying candidates with good potential. According to the report, the chosen candidates should, in addition to appropriate pharmacological properties:

- Be possible to synthesise
- Have a good intellectual property situation (i.e. be far from previous patents)
- Have good economic projections (based on cost and market estimates)
- Align with safety, health and environmental issues
- Have good chemical properties (solid state characterisation)
- Seem promising from scalability and technical engineering aspects (process design)

Each of the highlighted issues above has green chemistry relevance and therefore it is crucial that we as a green pharmacy community seek to engage with scientists in lead identification to facilitate good practice.

The use of high throughput screening is an example of where the pharmaceutical industry has been successful in identifying potential lead compounds whilst using less material, producing less waste and subsequently saving time (Tucker 2006).

Of the compounds of interest arising from high throughput screening, some may be removed due to so-called "structural alerts" based on human toxicity and side effects, for example cancer causing potential. There is also scope for highlighting potential synthesis difficulties at this stage also, and although traditionally process efficiency is not necessarily considered at this point, the report above indicates this could become increasingly important in future. Obviously this would not affect any decision to take the compound forward, but could indicate the need for parallel greener/novel synthetic routes at the earliest opportunity.

After screening/testing is complete, a compound is chosen to be taken forward as lead (possibly with a back-up). AstraZeneca are beginning to provide Persistence, Bioaccumulation and Toxicity (PBT) data for consideration on the compounds at this stage showing an increased awareness of environmental end-of-life concerns, although negative PBT data is by no means a fatal negative for the compound. This data would not necessarily assist in deciding between compounds from the same chemical family, which form the basis of a "lead series", as they often have similar properties (Oprea 2002). This therefore presents a difficulty in choosing between compounds based on their potential environmental impact, as they are likely to be related. Nevertheless, the earlier this type of information is provided, the sooner potential PBT issues can be highlighted and the greater chance of being able to make changes and work towards alleviating them.

Lipinski's Rule of Five (Lipinski et al. 2001), used to evaluate the likelihood of human oral activity of chemical compounds by looking at molecular properties such as number of hydrogen bond donors and acceptors and molecular weight, is an important tool in identifying and optimising lead structures. The development of a parallel set of rules, which would evaluate the environmental acceptability of a drug molecule and provide guidance on the likely acceptable molecular properties to achieve this could be potentially highly beneficial. However, even if this was achieved, it could represent further restraints towards innovation, as has been argued

in the case of Lipinski's rules, which would exempt a number of successful drugs that are currently on the market.

4.4.2.2 Lead Optimisation/Medicinal Chemistry

The next stage in drug design is to identify Structure Activity Relationships (SAR) to determine which parts of the molecule are important to biological activity and which are not, and identify the pharmacophore i.e. the functional groups important for activity and their positions relative to one another. Medicinal chemists then synthesise analogues of the lead compound with the same pharmacophore to increase activity and reduce side effects. Another objective for medicinal chemists is to deliver a compound that may be easily and efficiently administered to the patient.

If medicinal chemists can be engaged to successfully incorporate green chemistry principles and practice into their work, this will strongly influence the environmental impact of drug design. In a paper on the pharmaceutical perspective of green chemistry, Pfizer R&D describe pharmaceutical green chemistry beginning with medicinal chemistry and furthermore go on to say that "Chemists are highly creative individuals and when provided with the new guidance they have proved willing to adopt or invent new, greener practices" (Alfonsia et al. 2008).

A possible strategy for designing greener pharmaceuticals could be to look outside of the pharmacophore to identify any potential structures/functional groups that could cause environmental issues e.g. persistence, and design these out at an early stage. Similarly introduction of such groups could be avoided when synthesising analogues of the lead compound. The key issue for this would be how to identify such groups. This could potentially be done by QSAR (Quantitative Structure-activity Relationships). AstraZeneca reported at the CleanMed Europe Conference in 2006 that Persistence, Bioaccumulation and Toxicity (PBT) data are not used as a design criteria for human medicines, but they are beginning to use PBT information derived from QSAR and screening tests as early warning alerts. In theory, this strategy should not affect the activity of the compound. However this could be the case if, for example, that particular part of the molecule was involved in other interactions within the target, such as via a hydrophobic pocket.

Although this strategy may not be straightforward, a parallel consideration, i.e. the avoidance of groups known to be susceptible to producing toxic metabolites, is often taken into account when designing potential drug candidates (e.g. aromatic nitro groups, aromatic amines, bromoarenes, hydrazines, hydroxylamines or polyhalogenated groups).

Another challenge is to engage medicinal chemists in green chemistry thinking and practice. It has been noted that whilst many green chemistry principles are "second nature to process development chemists and their manufacturing colleagues, the same cannot be said of their medicinal chemistry colleagues" (Hjeresen et al. 2002). The need for rapid synthesis of analogues, often presents a barrier to inclusion of other considerations when designing synthetic routes. Tried and tested methodologies are preferred and the priority is to synthesise the target compounds as quickly possible to produce enough sample for testing. This may be to the detriment of efficiency and can often use reagents that would not be suitable on a larger scale due to

safety issues. A multi-dimensional approach of education and training, and the provision of appropriate tools that are simple to use in everyday laboratory practice, are likely to be required to encourage medicinal chemists to incorporate consideration of minimising environmental impact into their roles. For example, development of a tool that allowed reaction methods for particular chemical transformations to be ranked in terms of "greenness" would perhaps be a good way of engaging medicinal chemists.

4.4.2.3 Candidate Selection

The ultimate goal for incorporating green credentials into key decision points during drug design would be to give consideration to these issues at candidate selection. Should a situation arise where there are two equally as promising and effective candidate molecules, consideration of their "green credentials" could become one of the factors for selection. There are a multitude of other factors that are likely to take precedence over environmental concerns, however if consideration of green credentials could be better embedded in earlier stages as described above this may assist with providing information on these issues as well as supporting a move towards realising this goal.

4.5 Manufacturing and Production

4.5.1 Process Chemistry

Process chemistry is arguably the area where most of the effort towards incorporating green chemistry has been achieved to date. Process chemists should therefore be encouraged to work more closely with medicinal chemists in order to transfer skills and knowledge. They could become involved at an earlier stage, perhaps working to design parallel greener synthetic routes to promising lead compounds or components of these compounds e.g. the pharmacophore. Should green credentials be considered during lead identification, the need for an alternative greener route to be developed in parallel could be flagged up at an earlier stage. Synthetic routes developed in medicinal chemistry often have to be completely redesigned by process chemists, and hence earlier involvement in the synthesis is likely to save time (and therefore money). Greater focus on the environmental profile of syntheses at this stage could also provide benefit through reduction of costs associated with making changes, especially to process improvements, in particular after approval.

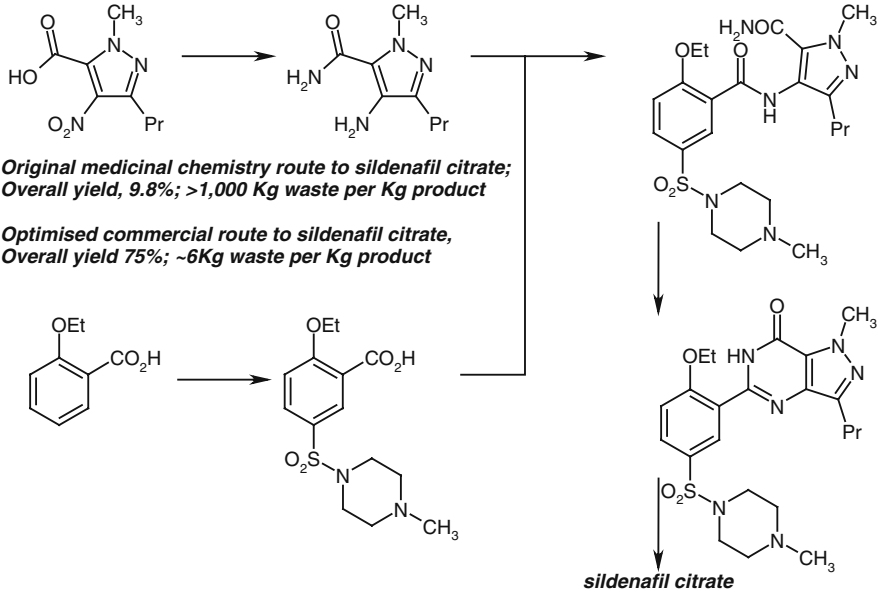
4.5.1.1 Process Chemistry: Clean Synthesis

Although the complex nature of pharmaceuticals could be seen by some as a disadvantage towards adopting green chemistry techniques, the diverse range of theoretical routes to synthesise pharmaceutical products actually provides greater flexibility in choice of starting materials and reagents. This enables the incorporation of green chemistry techniques and potentially "green" selection and decision criteria, allowing the product to be made without affecting its performance whilst at

the same time improving its environmental profile (Hjeresen et al. 2002). Clean(er) synthesis of pharmaceutical products can be achieved through the application of green chemistry techniques, for example the better use of catalysis, reduction in the number of synthetic steps and minimisation of waste, use of novel energy efficient methods and the use of alternative synthetic routes avoiding chemicals of concern.

One way of achieving a reduction in resource consumption and waste is to avoid unnecessary derivitisations and minimise the use of protection and deprotection steps. Chemists at Scripps Research Institute have recently demonstrated that it is possible to synthesise complex natural products without the use of protecting groups, reducing the number of steps and obtaining a higher overall yield of the final product (Baran et al. 2007, O'Malley et al. 2007). In an analysis of the reactions used for the preparation of drug candidate molecules carried out by GlaxoSmithKline, AstraZeneca and Pfizer, protection and deprotection steps accounted for 6 and 15% of the total chemical transformations respectively (Carey et al. 2006). These steps represent significant resource demands and waste generation, however 35% of the syntheses were achieved without the use of protecting groups. Strategies for avoiding unnecessary derivitisation during earlier synthetic routes, for instance those developed in medicinal chemistry would be advantageous.

The Pfizer Viagra^{TM} (sildenafil citrate) synthesis has been referred to as the "industry gold standard" for reduction in waste (Kuzemko et al. 2007). The newly developed route adopting a range of green chemistry techniques reduced the amount of waste produced to just 6 kg per kg product; cf pharmaceutical industry standard of 25–100 kg (Dunn et al. 2004).

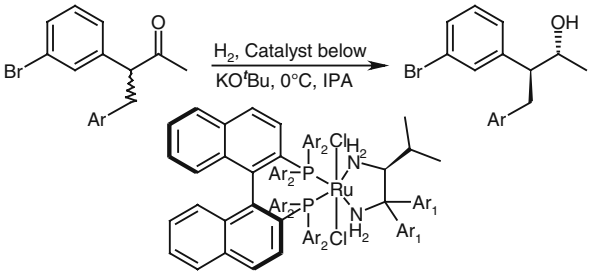


Work-up and isolation of reaction intermediates typically carries a large environmental burden through the use of solvents, energy and other materials. Synthetic chemists traditionally rely on standard workup procedures to isolate products e.g. extraction and chromatography. In commercial production, these procedures can be

very costly in terms of labour, capital and waste disposal. A strategy has been developed to gather physicochemical data to identify reaction conditions that can also be used for workup and isolation, for example changing reaction solvent could allow product to crystallise out of solution, allowing isolation by simple filtration rather than extraction (Rouhi 2002). Telescoping stages together can also reduce energy usage by avoiding the need to isolate intermediates (Carey et al. 2006) and the use of telescoping reactions as part of the strategy to synthesise important intermediates has also been reported (Connolly et al. 2005).

The benefits of applying catalytic methods for syntheses to reduce the environmental impact and increase the resource efficiency of the pharmaceutical industry are numerous. The use of catalytic rather than stoichiometric reagents can dramatically decrease the amount of raw materials used, waste generated and enhance the atom economy of a synthesis, as well as saving time and often energy. The development and application of catalytic methodologies are described as a powerful tool to improve both the economic and environmental profile when designing synthetic routes within process R&D (Federsel 2006).

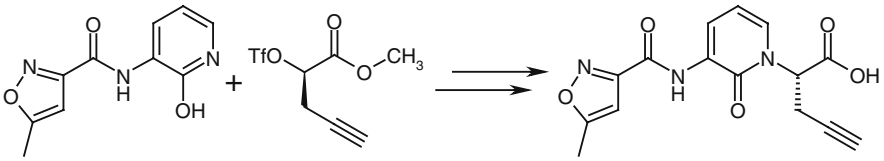
A particularly important area of catalysis is asymmetric catalysis, and in particular dynamic kinetic resolution can lead to much improved clean syntheses. For example, researchers at Merck have utilised a dynamic kinetic resolution hydrogenation strategy in the synthesis of the anti-obesity drug taranabant (Chen et al. 2007). Thus dynamic kinetic resolution under hydrogenation conditions using ((S)-xyl-BINAP)((S)-DAIPEN)$RuCl_2$ was used to set two stereogenic centres in a single step from a racemic ketone, giving an alcohol with improved stereoselectivity of 93–94% ee and a 9:1 ratio of diastereomers after optimisation.



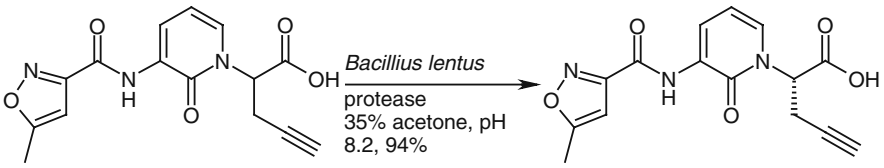
Another new area of catalysis that is gaining recognition and acceptance is organocatalysis: the advantage being that, as no transition metal ions are involved, there are no safety issues with respect to heavy metal residues in intermediates and/or final products, in addition to making waste streams easier to treat (Gaunt et al. 2007). Some of these transformations now rival transition metal catalysed reactions in terms of selectivity and yield, however catalyst loadings are generally quite high (typically ~20%).

Biocatalysis is becoming a much more utilised and trusted technology for chemical synthesis as a result of recent advances in biology, protein expression, high

throughput screening, and enzyme evolution technologies. To truly impact chemical synthesis at the industrial scale, enzyme discovery, biocatalyst optimisation, process design and development must be integrated in order to deliver cost-effective and green chemistry solutions for drug manufacture (Tao et al. 2007). There are a number of examples where a biocatalytic process has replaced a traditional chemical synthesis. In the synthesis of AG7404 (a rhinovirus protease inhibitor for treatment of the common cold) a key step was alkylation of an enantiomerically pure triflate by a pyridonyl amide followed by ester hydrolysis to the acid.



The issue with this approach is that the chiral triflate was prohibitively expensive and so an alternative approach was sought. Synthesis of the racemic ester was relatively trivial and substantially less expensive. Treatment of this material with *bacillus lentus protease* (BLP) resulted in kinetic resolution of the material with the desired product being isolated in 50% yield and 96% ee. Furthermore, the undesired enantiomer could be racemised and recycled into the process again thus increasing overall conversion.



The second-generation chemoenzymatic process gave higher yield than the first-generation alkylation route (Dragovich et al. 2003).

4.5.1.2 Process Chemistry: Solvents

The pharmaceutical industry has, in the last number of years, made enormous strides in the minimisation of solvent usage. For example, a new process has been adopted by Pfizer for Lyrica® manufacture which is not only significantly cheaper, but will eliminate up to 5 million gallons per year of solvent usage.[3] Pfizer also set a public goal to further control Volatile Organic Compound (VOC) emissions by committing to reduce releases by 40% on an absolute basis from the baseline year of 2002 by

[3] http://www.pfizer.com/files/corporate_citizenship/cr_report_2007.pdf

the end of 2008: this target was met 2 years in advance due to an aggressive solvent reduction program, production changes and installation of additional thermal oxidizer units.

Similarly, in 2004, GSK reported that total VOCs emitted to air decreased by 16.4% since 2003 (20.0% since 2001). VOCs emitted to air per unit sales decreased by 12.1% since 2003 (19.6% since 2001). However, in 2007 GSK did not meet its targets for VOC releases to air; this was due to product mix changes in some processes causing solvent recovery equipment at some of the manufacturing sites to be inadequate to completely capture and recycle certain solvents used in the process.[4] This demonstrates that although advances have been made this aspect still requires attention.

However, more importantly each of the major pharmaceutical companies has developed its own in-house solvent selection tools and one of the major factors in this selection process is environmental impact. Pfizer have developed a system of classifying solvents as red, orange or green. Red solvents are those that are to be avoided if at all possible due to health and safety issues, although the environmental impact is also a consideration. The green solvents are those that are safe to use and have minimal impact on the environment with orange being somewhere between these two extremes. This approach is being rolled out to a reagent selection tool also. GSK have a similar solvent selection process with similar classifications.

Since the beginning of the Green Chemistry movement 10 years ago, the need for alternative solvents for reactions has been one of the major issues to be faced, and the classification of the "greenness" of a solvent is a matter of much debate. Clark and Tavener made a significant contribution to the debate by evaluating each of the classes of "green" solvents against key properties: ease of separation/reuse, health and safety, cost and environmental impact (Clark and Tavener 2007). This resulted in a score for each of the class of solvents. However, this does not tell the whole story as, for example, some ionic liquids have since been shown to have unfavourable toxicity profiles, and so the criteria for "greenness" is always changing. Similarly biosolvents such as ethanol, butanol, isosorbide, dimethylisosorbide, diethyl lactate, methyl tert-butyl ether and 2-methyltetrahydrofuran are becoming available and have improved Life Cycle Assessments (LCAs) due to their derivation from renewable resources. As a general rule there are many bio/alternative solvents available for some chemistries and extraction, but there is still a desperate need for dipolar aprotic solvents with reduced environmental impact with respect to DMF (dimethylformamide), DMSO (dimethyl sulfoxide) and NMP (N-methylpyrrolidone).

4.5.1.3 Process Chemistry: New Technologies

In-house industry tools have been developed by the pharmaceutical industry to facilitate selection of green technologies. For example, GSK have published a guide

[4] http://www.gsk.com/responsibility/environmental-sustainability.htm

to allow scientists and engineers adopting lifecycle considerations to make comparisons between traditional and emerging technologies based on environmental, safety, efficiency and energy perspectives, with a view to considering economic factors in future (Jiménez-González and Overcash 2000, Jiménez-González et al. 2002).

Microwave technology has been used in research chemistry for the best part of 20 years, however there still seems to be intransigence on the part of both the chemical and pharmaceutical industries to take this technology to full-scale production. It is perceived by the industry that scale up of microwave chemistry is a problem. However, there are reports that reactions can be carried out on a relatively large scale. For example a green approach to N-heterocyclisation reactions ranging in scale from 20 mmol to 1 mol performed under microwave irradiation in open vessels has been investigated. By using water as the solvent and no transition metal catalysts, N-heterocycles are formed in a fraction of the time needed for conventional synthesis of these compounds (Barnard et al. 2006).

It should also be noted that there are many very large-scale and continuous microwave apparatus manufactured for other applications, such as treatment of sludge and drilling muds and that technology transfer to chemical synthesis is a strong possibility. The use of microwave processing to treat complex waste streams from drug manufacturing is also a possibility.

One of green chemistry's goals is to have selective reactions that require minimal auxiliaries to induce that selectivity. Biotechnology is ideally suited to meet these demands. Furthermore, the reactions are often carried out in a predominantly aqueous environment thus minimising environmental impact of the solvent for the reaction as well, and hence the synergy of these technologies is notable. However, some areas of the pharmaceutical industry are rather disinclined to use biotechnology. This is most likely down to the views of the "traditional organic chemist" who may see these transformations as something of a "black art" where the process either works perfectly or not at all. However, there are examples in the literature where biotechnological processes have started with poor yields and selectivities, which after optimisation (solvent system, genetic engineering, pH, co-factors etc.) have given quantitative yields and selectivities of greater then 95%.

It is estimated that the ratio of biotechnological to chemical production processes of pharmaceutical compounds is 1–10. In a study of the consequences, opportunities and challenges of modern biotechnology for Europe, the application of biotechnologies in the manufacturing of healthcare products may have a positive impact on the environment via improvement of resource and energy use and reduction of pollutants and generation of waste. One example of where this is currently being employed is in the manufacturing of antibiotics, for example cephalosporin.[5]

[5] http://bio4eu.jrc.es/documents/eur22728en.pdf

4.6 Product Use and Fate

4.6.1 Drug Efficacy and Delivery as Green Pharmacy

Green Chemistry may also be applied to develop alternate drug mechanisms and improve drug efficacy. For example, green chemistry could provide complementary techniques to assist the rapidly growing area of biopharmaceuticals.

Scientists at the University of Nottingham have been working on a process to develop polymer drug coatings from biodegradable plastics using supercritical carbon dioxide technology.[6] This research could find particular application for encapsulating biopharmaceuticals, the active components of which could be damaged by using traditional coating methods, as they can employ high temperatures and/or volatile and potentially toxic solvents (which obviously also have environmental implications). This method of drug delivery also has the added advantage of maximising the effect of the drug by controlling its release over a set time period, reducing the number of injections required by the patient. Once introduced into the body these biodegradable polymers are degraded into soluble, non-toxic by-products. Different polymers degrade at different rates providing further flexibility for release rates. This work could have wide potential scope for drug encapsulation techniques.

Although up to now the major, almost exclusive, focus of research efforts have been on the primary manufacture of the API it should be noted that the product a consumer actually purchases often only has the API as a minor component. The API is usually contained within a number of excipients, which may be cellulose, lactose, etc. if the pharmaceutical is in the form of a tablet, or maybe in aqueous solution with glucose, glycerol, surfactants etc. and each of these will have an environmental impact.

Although as raw materials these have good environmental credentials the overall secondary manufacturing process for a tablet (outlined in Fig. 4.4) process can have significant impact.

Using data provided by a pharmaceutical manufacturing company we were able to evaluate the entire secondary manufacturing process in terms of its environmental impact with a particular interest in the energy use, water consumption, emissions to air and water as well as waste generation.

From this study a carbon footprint for each of the process steps was calculated (Fig. 4.5) and a number of areas were identified as process “hot-spots”:

As can be seen the major carbon footprint comes from keeping the room at the appropriate temperature and humidity to enable successful tableting, along with a serious environmental burden of waste generation. The majority of this waste carbon footprint is as a result of having to destroy (slightly) contaminated water, mostly from cleaning the equipment, by incineration.

---

[6] http://www.physorg.com/news108908353.html

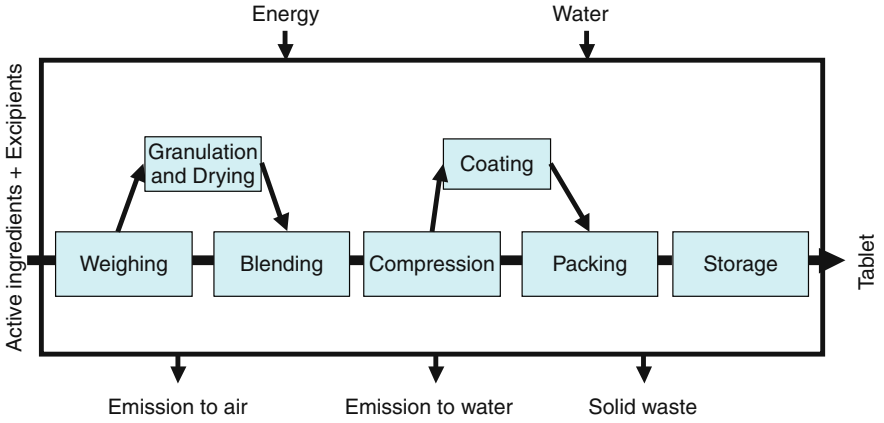
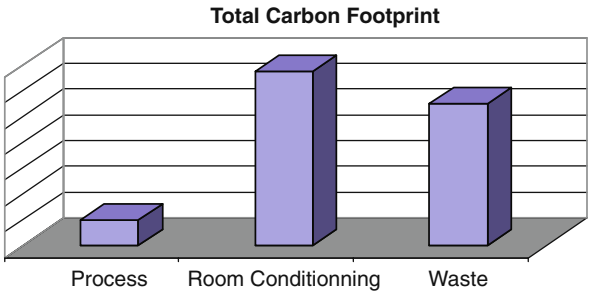


Fig. 4.4 The secondary manufacturing process for production of a tablet

Fig. 4.5 Carbon footprint of a tabletting process



4.6.2 End-of-Life Issues

Although not the focus of this chapter a few comments should be made to put this into the wider context of green pharmacy.

An important principle of green chemistry is designing chemicals and products to degrade at a reasonable rate after use, so that they do not accumulate in the environment. Designing drugs that are degradable is a contentious issue as the biological activity of a pharmaceutical compound is dependant upon its precise chemical structure and must also have the correct level of stability and a reasonable shelf life. Examples of biodegradable and photo-labile drugs in the literature whilst promising, appear to have been discovered serendipitously and not as the result of incorporating these properties into drug design (Lee et al. 2000, Kümmerer et al. 2000).

In their review "Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry", Khetan and Collins report that the ideal method for preventing the issue of pharmaceuticals in the environment would be to develop

new drugs that incorporate an additional criterion which upon release to the environment would lead to their rapid removal (Khetan and Collins 2007, Kümmerer 2007). Suggested methods for doing this include:

- Incorporation of a "chemical switch" built into the drug, which upon activation (outside of the body) would lead to rapid decomposition
- Attachment of "affinity groups" to the drug that could lead to quantitative sorption on a particular support to be used at treatment plants

However the authors of this article do acknowledge that the complex balance of pharmacodynamics and pharmacokinetics of drug molecules could mean that "searching for panaceas to persistent pharmaceuticals may simply be hoping for the impossible".

However this does not mean there is no scope for incorporating such issues into drug design. Approaching the issue from an alternate angle, i.e. designing persistence out rather than designing degradability in, may be another way to tackle this issue. Obtaining a suitable balance between the required stability in the body, for example in terms of hydrolysis and drug metabolism, and the desired degradability in the environment is a major challenge. Nevertheless, since the potential for degradation of pharmaceuticals greatly varies across their life cycle (i.e. different pH, temperature, redox conditions, bacteria and enzymes present), stability during the application phase and degradability thereafter are not necessarily mutually exclusive (see Kümmerer, Chaps. 1 and 9, this book and Kümmerer 2007).

The pharmaceutical industry could benefit from cross-sectorial knowledge transfer from the agrochemical industry, which has long been subjected to tight regulation with regard to the end of life of their products and had to develop less persistent products, which balance agricultural needs with environmental and health issues.

One strategy for promoting the consideration of Persistence, Bioaccumulation and Toxicity (PBT) characteristics of pharmaceutical products is the Swedish Classification Scheme developed in 2005 by the Swedish Association of Pharmacy Industries (LIF), the Swedish Medical Products Agency, Apoteket, the Swedish Association of Local Authorities and Regions and Stockholm County Council (see Wennmalm and Gunnarsson, Chap. 16, this book).[7] This voluntary scheme looks at environmental hazard and associated risk of pharmaceutical products. Different levels of information are provided depending upon level of expertise (e.g. patient vs. prescriber). AstraZeneca advise that where this scheme is having most effect is in the procurement of bulk drugs, for instance in hospitals, rather than by the patients themselves requesting information on the environmental profile of drugs prescribed to them. Although the scheme is only operational in Sweden at present, there is a likelihood that it will be rolled out across Europe in future and hence could provide an incentive for pharmaceutical companies to look more closely at the PBT credentials of their products. Should this be the case, it would be an important opportunity

[7] http://www.lif.se/cs/default.asp?id=12620

for the pharmaceutical industry to additionally lobby for the inclusion of consideration of the environmental impact of how the drug was made (including the raw materials, drug synthesis and formulation), in addition to its hazard/risk profile at the end of life, as this would also be a significant issue when making comparisons between different pharmaceutical products as well as between manufacturers of the same product.

4.7 Engaging Key Stakeholders Across the Lifecycle

4.7.1 The Perceived Problem of Green Pharmacy?

The three main parameters considered by the regulatory bodies during drug approval are efficacy, safety and quality. In the EU an Environmental Risk Assessment must now accompany an application for a marketing authorisation for a medicinal product for human use (the situation for veterinary medicine is different). However, in reality this still does not drive the need for incorporation of green pharmacy and consideration of environmental impact into drug design, as negative environmental impact "should not constitute a criterion for refusal of marketing authorisation".[8] Refusal of drug authorisation based on the ERA would be perceived to represent an unacceptable barrier to innovation within the pharmaceutical industry. Instead, specific arrangements to limit impact are made on a case-by-case basis, for example, through precautionary and safety measures for administration, disposal and labelling.

The integration of green pharmacy and environmental thinking into drug design may also be considered by some to represent yet another hurdle to be overcome and hence face resistance. This may also be the result of lack of understanding about available tools and their benefits. In addition to raising awareness of opportunities available, one way of tackling this would be to provide incentive and encouragement, and an element of choice rather than enforcing new practices and putting obligations in place.

The high rate of attrition of drug compounds is another major barrier to innovation. The process of designing, developing and manufacturing active and safe drugs is an extremely difficult and time-consuming process. It is estimated that approximately one in a million compounds (or more) from those initially tested by high throughput screening is likely to make it onto the market (Oprea 2002). According to GlaxoSmithKline "the challenge for the green chemistry community is to develop systematic approaches to introduce greener practices so that the rate of attrition has less of an impact on preventing the introduction of greener practices". They believe that this needs to be done by balancing the attrition rate with the speed to market and introduction of green pharmacy early when costs are lower.

Patent life and hence speed to market is another major barrier to incorporating new techniques, technologies and ways of thinking. The industry values reliability

[8] EMEA Committee for Medical Products for Human Use (CHMP).

in its chosen methodologies, and new, greener practices may be viewed as risky or too time consuming. Regulatory pressure in terms of quality and safety of pharmaceutical manufacture potentially leads to perceived risks in adopting new practices over tried and tested methodologies. Therefore opportunities for reducing time and cost through the exploitation of these practices must be demonstrated, as well as the provision of internal support to allow the establishment of their reliability and also applicability throughout the business.

Other barriers for incorporating green pharmacy and minimising environmental impact into drug design may come from lack of internal support for such initiatives or poor internal communication.

4.7.2 The Opportunity of Green Pharmacy?

Regulators obviously have the greatest potential to promote the incorporation of green pharmacy and consideration of environmental impact into drug design and hence a strategy to encourage their awareness, involvement and commitment to these issues is essential. Ultimately, the ideal way to incentivise and therefore encourage consideration of green pharmacy and environmental impact into drug design, would be if this lead to an extension in patent life for the product.

A major driver for the better implementation of current activities and to introduce new ideas would be to engage high level management within the pharmaceutical industry on environmental issues and their risk to the business, demonstrate how green pharmacy can begin to address these issues, and make them part of the company's strategic plan. Building a business case for the implementation of green pharmacy practices would be a valuable step towards overcoming internal barriers.

The commercial side of the business should be better aligned with the drive towards implementing green chemistry, in particular giving scientists the opportunities to work with new, perhaps unfamiliar green technologies and other developments.

Methodologies are needed to link green chemistry practices more closely with corporate sustainability goals, and to extend the responsibility for sustainability outside of environment, health and safety departments. One approach is to have champions within R&D to lead this area, raise awareness within the company of the benefits of adopting such practices both from a commercial and environmental standpoint, and support those beginning to work towards the incorporation of green pharmacy practices. A number of the larger pharmaceutical companies have in-house green chemistry teams. The challenge is to get pharmaceutical scientists to see that these initiatives are applicable to everyone, and not just the dedicated team, through awareness, education and training.

This will necessitate more detail of the quality and type of information required as well as understanding at what stages it would be useful. Due to increasing demands on pharmaceutical scientists and decreasing budgets, GSK believe that in future there will be a greater reliance on "easily accessible, company-wide tools that

provide early assessments and highlight sustainability issues". One way of raising awareness could be to provide internal incentives, for instance via award schemes such as Merck's Environmental, Health and Safety (EHS) Chairman's Awards for Sustainability.[9] However there is also a need to lobby for external organisations and perhaps regulatory bodies to provide additional external incentives, for instance through extension of patent life for genuinely green and sustainable pharmacies.

4.8 Conclusions

Given the trend towards providing the consumer with environmental-related information (often on product packaging), be it announcing the absence of certain undesirable chemicals, the assurance of the working conditions of those involved in upstream manufacturing or the actual products carbon footprint, it may only be a matter of time before we see similar information on over-the-counter (OTC) drugs.

However, the NHS publication has clearly shown that while the possible harmful effects of drugs when they enter the environment cannot be ignored and requires greater vigilance and stewardship post-pharmacy, a major part of the environmental impact of a drug is pre-pharmacy and here the individual consumer at the counter and, more dramatically, the major health provider such as the NHS, can have a major role. Thus we now have a number of drivers that are coming together:

- Customer pull, both from the consumer in OTC and the NHS for prescription pharmaceuticals, incentivising the industry to become more sustainable
- Regulator push to try and minimise environmental impact, both under REACH and by the beginnings of some consideration being given to environmental impacts of manufacture
- Governmental targets to reduce both the industry's and the country's carbon footprint

Thus with these incentives and the myriad of available tools to mediate change, along with the potential rewards that would result, in both environmental and now financial terms, the attainment of a green and sustainable pharmacy is a real possibility.

References

Alfonsia K, Colberg J, Dunn PJ, Fevigd T, Jennings S, Johnson TA, Kleine HP, Knight C, Nagy MA, Perry DA, Stefaniakc M (2008) Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. Green Chem 10, 31–36

Anastas P, Warner J (1998) Green Chemistry: Theory and Practice. Oxford University Press, Oxford

[9] http://www.merck.com/cr/environment_health_and_safety/

Andraos J (2005) Unification of reaction metrics for green chemistry II: Evaluation of named organic reactions and application to reaction discovery. Org Process Res Dev 9, 404–431

Baran PS, Maimone TJ, Richter JM (2007) Total synthesis of marine natural products without using protecting groups. Nature 446, 404–408

Barnard TM, Vanier GS, Collins MJ (2006) Scale-up of the green synthesis of azacycloalkanes and isoindolines under microwave irradiation. Org Process Res Dev 10, 1233–1237

Carey JS, Laffan D, Thomson C, Williams MT (2006) Analysis of the reactions used for the preparation of drug candidate molecules. Org Biomol Chem 4, 2337–2347

Chen C-Y, Frey LF, Shultz S, Wallace DJ, Marcantonio K, Payack JF, Vazquez E, Springfield SA, Zhou G, Liu P, Kieczykowski GR, Chen AM, Phenix BD, Singh U, Strine J, Izzo B, Krska SW (2007) Catalytic, enantioselective synthesis of taranabant, a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity. Org Process Res Dev 11, 616–623

Clark JH, Smith P (2005) Basic principles of green chemistry. Innov Pharma Technol, 94

Clark JH, Tavener SJ (2007) Alternative solvents: Shades of green. Org Process Res Dev 11, 149

Connolly TJ, McGarry P, Sukhtankar S (2005) An eco-efficient pilot plant scale synthesis of two 5-Substituted-6,7-Dimethoxy-1-H-Quinazoline-2,4-Diones. Green Chem 7, 586–589

Dragovich PS, Prins TJ, Zhou R, Johnson TO, Hua Y, Luu HT, Sakata SK, Brown EL, Maldonado FC, Tuntland T, et al. (2003) Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 8. pharmacological optimization of orally bioavailable 2-pyridone-containing peptidomimetics. J Med Chem 46, 4572–4585

Dunn PJ, Galvin S, Hettenbach K (2004) The development of an environmentally benign synthesis of Sildenafil Citrate (viagra) and its assessment by green chemistry metrics. Green Chem 6, 43–52

Federsel H-J (2006) In search of sustainability: Process R&D in light of current pharmaceutical industry challenges. Drug Discov Today 11, 966–974

Gaunt MJ, Johansson CCC, McNallya A, Voa NT (2007) Enantioselective organocatalysis. Drug Discov Today 12(1/2), 8–27

Hjeresen DL, Kirchhoff MM, Lankey RL (2002) Green chemistry: Environment, economics, and competitiveness. Corporate Environ Strategy 9(3), 259–266

Jiménez-González C, Constable DJ, Curzons AD, Cunningham VL (2002) Developing GSK's green technology guidance: Methodology for case-scenario comparison of technologies. Clean Tech Environ Policy 4(1), 44–53

Jiménez-González C, Overcash M (2000) Energy sub-modules applied in life-cycle inventory of processes. Clean Products Process 2, 57–66

Khetan SK, Collins TJ (2007) Human pharmaceuticals in the aquatic environment: A challenge to green chemistry. Chem Rev 107(6), 2319–2364

Kümmerer 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 Chem 9, 899–907

Kümmerer K (2008) Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks. Springer, Germany

Kümmerer K, Al-Ahmad A, Bertram B, Wießler M (2000) Biodegradability of antineoplastic compounds in screening tests: Influence of glucosidation and of stereochemistry. Chemosphere 40, 767–773

Kuzemko MA, Van Arnum SD, Henry J, Niemczyk HJ (2007) A green chemistry comparative analysis of the syntheses of (E)-4-Cyclobutyl-2-[2-(3-nitrophenyl)ethenyl] Thiazole, Ro 24-5904. Org Process Res Dev 11, 470–476

Lee W, Li Z-H, Vakulenko S, Mobashery S (2000) A light-inactivated antibiotic. J Med Chem 43, 128–132

Lipinski CA, Lombardo F, Dominy BF, Feeney PJ (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 46, 3–26

Ng R (2004) Drugs: From Discovery to Approval. Wiley-Liss, Hoboken, NJ
O'Malley DP, Li K, Maue M, Zografos AL, Baran PS (2007) Total synthesis of dimeric pyrrole−imidazole alkaloids: Sceptrin, Ageliferin, Nagelamide E, Oxysceptrin, Nakamuric acid, and the Axinellamine carbon skeleton. J Am Chem Soc 129, 4762–4775
Oprea TI (2002) Current trends in lead discovery: Are we looking for the appropriate properties? J Comput Aided Mol Des 16, 325–334
Patrick GL (2001) An Introduction to Medicinal Chemistry. Oxford University Press, Oxford
Rouhi M (2002) Green chemistry for pharma. C&EN Sci Technol 80(16), p30–p33
Sheldon RA (2007) The E factor 15 years on. Green Chem 9, 1273–1283
Tao J, Zhao L, Ran N (2007) Recent advances in developing chemoenzymatic processes for active pharmaceutical ingredients. Org Process Res Dev 11, 259–267
Tucker JL (2006) Green chemistry, a pharmaceutical perspective. Org Process Res Dev 10, 315
Werpy T, Petersen G (eds.) (2004) Top Value Added Chemicals from Biomass: Volume 1 — Results of Screening for Potential Candidates from Sugars and Synthesis Gas. National Renewable Energy Laboratory, Golden, CO

Chapter 5
Creating a Sustainability Culture – A (Human Resources) Management Perspective for Sustainable Pharmacy

Michael Läufer

5.1 Introduction: From Crisis to a New Business Platform

Given today's worldwide financial crisis, there was never a more appropriate moment to reflect on the relevance of Sustainability in businesses! Since future generations will mainly have to bear the costly results of the far too short-term, non-sustainable focus of many business leaders, now is the time to push the envelope towards a much more sustainable approach across the entire value creation chain; now is the time to onboard for a significant change in the way we do business.

The primarily technical, scientific scope of this book provides a great opportunity to add a (Human Resources) Management perspective in order to support the practical application of Sustainable Pharmacy.

A few questions to act as a guide through this chapter:

- What are we talking when we spell the word Corporate Social Responsibility (CSR) or Corporate Sustainability? An attempt will be made to put various terms in operational perspective.
- Can any responsible business leaders afford to invest scare resources in addressing societal issues and why should any corporation take this on now?
- Once we have passed the rhetoric about Sustainability, what are the challenges, what are the practical solutions at hand?
- What is it that the Human Resources function can offer to help drive Sustainability across the business landscape?

Since addressing societal issues in general is not really a topic to provoke spontaneous support, a quote from Mahatma Gandhi should help us accept the rather long-term perspective of creating a Sustainability Culture:

> First they ignore you, then they laugh at you, then they fight you, then you win!

M. Läufer (✉)
LeadResource®, Global Human Resources Consultant, 79111 Freiburg, Germany
e-mail: mla@leadresource.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_5, © Springer-Verlag Berlin Heidelberg 2010

Embracing the concept of Sustainability with the commitment to put it into practice calls for deep breath and a good deal of persistence, as Sustainability is an ongoing management process without a final end.

The following will provide a good value proposition, yet it is far from self-selling.

Try "to Google" the word CSR or Sustainability and the results are overwhelming: Readings, conferences, company reports, consultancy offerings, and forums – you name it. The overflow on CSR-linked rhetoric is obvious, creating the impression, that in some cases CSR and the related topics are more a marketing fad, flavor of the month like, rather than credible communication. CSR rhetoric is still stronger than its reality; Ethical Branding has become a fast growing segment of the Marketing Industry.

The discrepancy between some window-dressing CSR commitments in glossy publications or Sunday Speeches, on the one hand, and activities with proven positive social impacts, on the other, has already created the term "Greenwashing" labeling those activities that are not grounded on sustainable behaviors and results, therefore lacking credibility.

On the other hand, whilst reality leaves enough room for improvement, reality in many cases is strong enough to allow for some rhetoric.

No doubt Sustainability has made its way up to the boardroom.

Responsible decision makers around the globe cross industries and public sectors have recognized this inescapable priority, calling sustainable development perhaps the largest challenge to mankind ever. Likewise, clients have been putting their stake into the ground, making Sustainability a key element for their buying decisions, not to mention the constantly increasing pressure from NGOs and other agents concerned about societal and environmental impacts of corporations.

5.2 Clarifying Some Terms

5.2.1 CSR, CC, CS

Corporate Social Responsibility/Corporate Sustainability Management being a relatively young management discipline and a fast developing topic at the same time, it is not untypical to see a multitude of fast changing terms, as well as buzzwords.

Whilst this is not the place for a comprehensive overview of the various academic discussions, three main terms are currently at the forefront of the political and corporate development:

- Corporate Social Responsibility (CSR)
- Corporate Citizenship (CC)
- Corporate Sustainability (CS)

The discussion started initially at the beginning of the twentieth century in the United States.

Later, in 1980 the Norwegian Prime Minister Gro Harlem Brundtland introduced a new definition of Sustainability:

> Meeting the needs of the present without compromising the ability of future generations to meet their own needs.[1]

Corporate Citizenship (CC) basically describes the role of companies as "good citizens", often considered as part of CSR, covering activities like corporate sponsoring, corporate volunteering, providing management or administrative support to NGOs or corporate community investment.

In 2001 the OECD called *CSR business' contribution to sustainable development. Consequently, corporate behavior must not only ensure returns to shareholders, wages to employees and product and services to customers, but they must respond to societal and environmental concerns and values.*[2]

Bringing corporation's economic, environmental and societal responsibilities together, the notion of the "triple bottom line" was born, creating a significant overlap with the concept of Corporate Sustainability (CS).

5.2.1.1 Corporate Sustainability Management

In line with the ambitious, forward-looking perspective of "Sustainable Pharmacy", Corporate Sustainability Management seems to be a most appropriate concept, along with the following comments, which will serve as the reference for the discussion to follow. Some of which will be elaborated upon later:

- CS is understood as the ability to manage economic, environmental and social effects to achieve sustainable development for the corporation and its core business, whilst at the same time creating a positive contribution to a sustainable development of the economy and society at large.
- As a holistic approach, CS attempts to systematically integrate social and environmental management with "regular" management activities. In contrast to CSR, where social and ecological issues are tackled as an additional task, CS embraces those activities as part of the core business, mobilizing core resources and expertise to create business cases for sustainability development.
- Voluntary as well as mandatory activities and compliance are considered part of CS, as are the dealing with issues presented by NGOs or customers.
- CS is not considered as giving something back to the society, kind of a profit-sharing scheme for the society – it is an integral part of doing business, thus a key element of the value creation chain.
- In a pro-active, innovative way, CS Management uncovers sustainable solutions without external requirement, taking the lead in developing sustainability

[1] WCED (1987).

[2] OECD (08 October 2001, Paris).

in all areas of corporate activities. In terms of Schumpeter's philosophy, CS destroys unsustainable products and markets, replacing them with more sustainable solutions. Eventually CS transforms into Sustainable Entrepreneurship.

5.2.2 Stakeholder Theory/Shareholder vs. Stakeholder Value

Corporate Sustainability is very much intertwined with another topic, which, due to the current financial crisis, has gained high profile: Shareholder Value versus Stakeholder Value.

This debate cannot be ignored since it has great impact on the business case for Sustainability to be discussed later.

The fundamental question here is: Can Sustainability only be realized at the expense of the economic value, which in the end pits business against society?

To say that the extreme focus on continually increasing shareholder value has badly failed is a humble description of what we see these days. Even the fiercest advocates of the shareholder value approach are now eating humble pie, calling for longer-term focus, admitting that maximizing shareholder value at the expense of the other stakeholders is not a good idea.

Already back in 1984 Freeman suggested that businesses build their strategy around their relationships with key stakeholders, therefore significantly widening the scope of corporate attention beyond the well-established focus on shareholder value.

He defines stakeholder as "any group or individual who can affect or is affected by the achievement of an organization's purpose" and in so doing, helps to clarify to whom a company is accountable, why and what kind of responsibilities it has towards those stakeholders.

Shareholders continue to be a key element of the stakeholder perspective, but at the same time it puts maximizing profit into a new perspective: profit is the result rather then the driver in the process of value creation, making money part of managers' goals, but not the only one!

Powerful examples of what can happen when corporations neglect their moral and legal obligation towards their stakeholders have been Shell's planned disposal of the Brent Spar oil platform in the North Sea or Nike's use of child labor in the production of their products. Both companies learned their lesson at great cost and changed their stakeholder management strategies, integrating a commitment to environment and social concerns into their core values.

The message here gives the answer to the question stated earlier: trying to realize economic value at the expense of the legitimate interests of key stakeholders is not only wrong from an ethical point of view, it is counter-productive and costly. The results of tunnel vision, where morality was considered irrelevant compared to the one goal of maximizing shareholder value can be studied in ethics-disasters like Enron or WorldCom, or the current banking crisis, just to quote a few examples.

5.2.2.1 Pharma's Stakeholder Perspective

On the other hand, looking at the Pharmaceutical Industry today, the concept of Stakeholder perspective seems to be already part of corporate management – for sure it is part of corporate communication:

> We engage our stakeholders, Our new stakeholder model helps build economic prosperity, At the core of our commitment to corporate responsibility are our stakeholders– the people who affect and are affected by our business actions. These include patients, physicians, regulators, customers, colleagues, investors, business partners and communities where we work and live, We are continuingly reviewing and improving our efforts to lessen our impact on the environment.[3]

> We aim. . . to understand and respond to stakeholder views, We seek to minimise the negative impacts and maximise the positive benefits of our business, Our approach to CR (Corporate Responsibility) . . . is essential to maintaining good relationships with our stakeholders. These in turn help us to achieve the goals of our business strategy and underpin the future sustainability of our business.[4]

Just these few sample quotes from Pfizer and GSK illustrate vividly, that the Pharmaceutical Industry over time has shifted its original focus on shareholder value to the much broader perspective of stakeholder interest, also demonstrated by their extensive reporting on CSR/CS activities.

Contrary to some critics, Corporate Sustainability and the related Stakeholder perspective is considered not as a hindrance to being profitable, but more so as an enabler to achieve sustainable economic value.

Besides the quoted examples from "Big Pharma", many other firms have already adopted the stakeholder view into their business practices.

To name a few: J&J, eBay, Google plus the companies featured in Collin's "Built to Last" and "Good to Great".

Obviously, some leaders and their teams are already on the move, driving their business with the strategic focus of Sustainability Development, ready and willing to take care of the legitimate interests of all key stakeholders, instead of just one of them. It should be interesting to understand what drives such significant change in corporate strategy so others can learn and translate the finding into their own situation.

5.3 Business Case for Corporate Sustainability

Everybody knows, that there is always a price to be paid, and the only question is when to pay it? For sure, the price for ignoring societal demands can only go up, but the business rationale for sustainability development goes beyond this.

Generally speaking, the motivation for any activity can be reduced to two fundamental drivers: to avoid bad or to do good.

---

[3] Pfizer (2007).

[4] GSK (2005).

Looking at the first motivator from the point of view of the Pharmaceutical Industry, it has been experiencing significant pressure over the past: regulations have grown tighter, chances to research, develop and finally market new pharmaceuticals have shrunk, public budget issues have increased cost sensitivity of healthcare systems everywhere, competition is fiercer than ever before leading to mergers and global consolidation of the market. On top of all this, pharmaceutical companies find themselves constantly in the limelight, confronted with a sometimes almost hostile attitude by NGOs or patient pressure groups (this being fair or not is another question), plus society's highly developed expectation to demonstrate environmental sensitivity. What applies for any company applies even more to this industry: Virtually every step of its activities along the value creation chain has an impact on the environment, especially the areas of research and development, production of its products and the societal impact of granting access to medications for underprivileged populations around the globe.

The general precept "to do good or to do no harm" seems to have mutated to "do maximum good and minimum harm". Consequently it is no surprise that more and more decision-makers pay closer attention of their stakeholders' concerns and expectations, thus the growing efforts to build an image of responsibility.[5]

Whilst "avoiding bad" is mainly of responsive nature, including the risk to give outside stakeholders control over the own business agenda, the second motivator "to do good" leads to a strategic approach, to what earlier has been called Sustainable Entrepreneurship.

The Stakeholder perspective fosters a shared purpose of the firm – to create values which others are willing to freely trade for. Doing such business effectively requires a full understanding of the needs of all affected parties, the stakeholders. In this approach, business leaders act as proactive developers, focusing on the integration of business and societal goals into the core.

It goes without saying, that each industry, each organization must identify its very stakeholders and at the same time clearly identify not only the most pressing societal priorities but those that intersect with its particular business.

As any corporation has only limited resources, the key is how to allocate them efficiently: does this cause present an opportunity to create meaningful benefit for stakeholders as well as strategic value for the business? This way Corporate Sustainability creates win-win situations yielding most significant positive societal impact and greatest business benefit at the same time.

As those societal impacts change over time, a well managed process, as for any strategic issue, is needed in order to identify and track evolving social effects in the future.

---

[5] For more info see various studies cited below, such as: Barth and Wolff (2009), Corporate Leadership Council (February 2006), IBM Institute for Business Value (2008), Oekom Research (2009), and Raman (2009).

5.3.1 Business Benefits as a Fact

The list of documented business benefits as a result of approaching sustainability prospects the same way, as core strategy is impressive, crossing big corporations as well as mid sized firms, industries, countries and continents.

With respect to the scope of this discussion, some examples will serve as prominent references to illustrate the areas of positive impact from credible Sustainability Management:

- Higher customer satisfaction and loyalty
- Positive impact on purchasing, better, long-term relationship with suppliers
- Improved company reputation
- Positive brand differentiation
- Receiving more trust from stakeholders
- Improved relations with regulators/legislation
- Being more attractive for investors
- Better risk management
- More fruitful dialogue, constructive cooperation with critical stakeholder groups
- Higher compliance in general and especially with environmental regulations
- Higher production efficiency and waste reduction
- Better quality products and processes
- More open climate fostering creativity, yielding more innovation
- Advantages in the "war for talent", higher attraction of talent
- Higher colleague engagement
- Better working conditions, improving workforce wellbeing
- Competitive advantage in general, due to doing things differently beyond best practices

Since we tend to prefer being convinced by financial terms, here a few performance indicators which have had a positive impact as reported across various studies as well as stated by business leaders during surveys:

- New revenue streams
- Productivity benefits
- Higher market share and market value
- Higher product value
- Brand premium
- Higher shareholder value
- More positive ratings from rating agencies
- Better access to new markets
- Lower insurance cost
- Lower capital cost
- Lower recruiting cost
- Lower cost due to lower employee turnover

5.3.2 Creating Win–Win

What's in it for the stakeholders? Again some examples:

- Improved products
- Improved healthcare
- Greater access to products and healthcare
- Increased corporate accountability
- Financial contribution to local, national economies
- Higher energy efficiency
- Improved raw material efficiency
- Reducing environmental impacts
- Reduced pressure on non-renewable resources
- Knowledge-building and improvements in supply chain
- Positive impact on employment
- Greater openness and success to address environmental and social issues proactively together with corporations
- Crafting new partnerships

5.3.3 Testimonials

And finally listening to a few Quotes:

> We believe, that good Corporate Responsibility can be a source of business innovation.
> To be responsible and accountable – socially, ethically and environmentally – is to be trusted. We need that trust. . . to support a sustainable enterprise.[6]
> Demonstrating that our practices are responsible and ethical benefits the business in the following ways: An improved reputation and trust in our products. The ability to attract, retain and motivate talented people. Constructive engagement with stakeholders. This helps us to prevent avoidable conflict and identify innovative approaches that benefit us and wider society. Greater access to markets.
> CR offers a *rational* argument to win customer loyalty and – confidence.[7]

There is growing evidence, that Corporate Sustainability (CS) and business is recognized as to be much more than a zero-sum game – there are plenty advantages stemming from Sustainability Development, if handled properly.

5.4 Implementation Challenges

As we are getting ready to apply the above, we had better hold our breath for a few more moments, looking at the challenges at hand that need to be dealt with on our journey to creating a Sustainability Culture within our organizations.

A few stand out from the lessons learned by those business leaders and academics who talk on the basis of real business experience and extensive studies:

[6] Pfizer (2007).
[7] GSK (2005).

5.4.1 Sustainability at the Core

The full integration of sustainability issues into the core business and its strategy is critically important, yet rather difficult to do in practice.

Allowing stakeholders to take over the business agenda ("those who scream the loudest, are the first to be served") is a remedy for failure just as it is to take Sustainability as a checklist of disconnected efforts.

In order to reap maximum benefit from Sustainability Development for both the business and the stakeholders, the company must know its own strengths and expertise, be clear on the above described intersections between its core business and the legitimate expectations of stakeholders and focus on those unique leverage points. Since strategy is about choices, this approach calls for clear-cut management decisions to align Sustainability issues with core business goals and for a long-term commitment prior to defining structures and allocating rare resources.

5.4.2 Communications and Transparency

Doing good and talking about it sounds pretty basic and in fact credible communication and transparency are fundamental elements of implementing and living a sustainability culture. It is also crucial to forge and maintain a fruitful dialogue and cooperation with stakeholders. As blogs, podcasts, text messages, YouTube, MySpace and most recently Twitter keep societal issues constantly "in the air", "Greenwashing" and "Window-dressing" will quickly be unmasked, backfiring and causing severe long-term damage to company reputation internally and externally.

Knowing how fast information travels these days and how valuable today's reputation is for future growth and for employer attraction, communication should rather move away from image and put the emphasis on substance, reporting on real impact rather than on anecdotal marketing activities.

In addition, the "need-to-know" criterion as basis for info sharing is obsolete. Only transparency can match the relentless pressure from all kinds of watchdog groups to get proper information about the entire life cycle of companies' activities. At the same time this creates the need to fully understand and anticipate stakeholders concerns and expectations. This way communication grows from information dumping to making it relevant for those key constituencies and helps build trust.

5.4.3 Metrics

Another area that differentiates those who realize Corporate Sustainability as a platform for growth from those who, despite good intentions, don't get the proper return on their investment is the area of measurement.

"What gets measured gets done" applies here too. Talking a good talk may impress people for a short time, but in the end the famous "so-what-question" needs to be answered based on results.

Linking Sustainability assessment with key performance indicators (KPIs) wherever possible is part of a systematic measurement over time. Tracking interdependency and results through a Balanced Score Card is an effective approach too, if the company can afford the necessary infrastructure in its controlling systems. In any case, the clearer goals are defined, the more they are open for qualitative and quantitative measurement, creating a solid base for credible reporting on social impact of Sustainability.

The above-mentioned examples of business cases show the lead – claiming those benefits must be monitored properly in order to get and maintain long-term support and commitment. Whilst success stories for sure are more popular for corporate publications, credibility can also be gained from admitting those efforts that trail behind expectations or have failed completely. In many cases the most powerful learning comes from analyzing failures or mistakes, being translated into powerful solutions for the future.

5.4.4 Changing Behaviors and Attitudes

The ultimate challenge is the appreciation that changing behavior and attitudes is at the heart of all the above. We are talking no less than driving sustainability values into the structure, processes and incentives that mould the behavior of the entire workforce, across all functions and hierarchical levels. So, how to move forward creating a Sustainability Culture?

5.5 Creating a Sustainability Culture

It all begins with knowing where to depart from and where the journey is supposed to get us to, identifying the key change agents, the barriers to change as well as the main change blockers, being clear on how change happens and putting a system in place that creates enough reference points to check on a regular basis if we are on track or not.

5.5.1 Culture Change

Without going into all the details of change management and revealing all managerial challenges of driving cultural change, a few remarks will shed some light into what we are dealing with here:

- Changing the strategy as discussed before requires changing the culture to support that strategy.
- Whilst company culture is recognized as a potential competitive advantage, it can also stifle change since those who have been comfortable with today's situation,

can take it as a threat to the status quo. This is especially relevant for organizations, with a proven track record – they need to overcome the potential tyranny of success in order to open the organization for the needed change.
Quoting Niccolo Machiavelly (The Prince, 1513):

> There is no more delicate matter to take in hand, nor more dangerous to conduct, nor more doubtful in its success, than to be a leader in the introduction of changes. For he who innovates will have for enemies all those who are well off under the old order of things, and only lukewarm supporters in those who might be better off under the new.[8]

- Building on the previous point: Communicating the strategic intend through a credible business case starts building commitment across the entire workforce. Before asking people to join the change effort, they must be clear on the rational and on what the perspective of a successful implementation of the change will look like, how it will be measured and how it will impact all stakeholders.
- Fundamental change like the one we are talking here needs powerful champions and sponsors who engage themselves visibly, consistently in words and actions and for the long haul.
  Having identified Corporate Sustainability earlier as a bottom-line imperative, it is crucial for real change to occur getting senior management buy-in.
  Once the executive team has signed up to the fact that this cultural change initiative is not going away like other "flavors of the month", the process can take off.
- Since such change is to occur within an already existing organization with its particular history, with its current business environment and with an existing culture, the aim is to change as much as necessary whilst at the same time taking advantage as much as possible of the current framework.

Painting a collectively shared picture of the actual culture is a good starting point. At the same time the corporate strategy, which now includes social and environmental dimensions as discussed above, must be set up and communicated in such a way that every colleague knows what it means for her/his day to day job.

Who is supposed to know the current culture best, who should be involved in translating the current values and its resulting behavioral attitudes into gaps between today's situation and the required future outlook? The employees come to mind first, they are the ones whose insights and input will largely contribute to realizing this change.

In addition, conducting a culture diagnosis is a perfect opportunity to rally the entire organization across hierarchies, functions, locations and all different groups of the workforce. Broad involvement and visible participation will foster colleagues' commitment and support all along the change initiative and steer their thinking and behavior when applying Sustainability in the daily routine later.

At the end of this culture diagnosis some of the current norms and values will have been reconfirmed as being instrumental for the future success, others will have

[8] Machiavelli (1985).

been identified as ineffective, whilst some new ones will have been added as critical for the future success. This way Sustainability will have been translated into a set of norms, values and behavioral attitudes describing the culture that fits the defined strategy best.

Unfortunately laminating those grand outcomes onto small cards, that everybody carries in their wallet, decorating the lobby, meeting rooms and pathways with glossy posters will not do the job of shaping the "software of the company"!

5.5.2 Wanted: Role Models

A prominent lever to promote the needed norms and values is using management behavior to convey vivid messages about attitudes and behaviors, often referred to as "walk the talk". It is free of charge, but very effective, using the senior management team as "signal givers" to demonstrate every day what is appropriate and what is not, what is important and what not.

In general, but especially in times of change, this group is closely watched by the rest of the organization and their credibility is constantly tested. If people receive a consistent message through what they observe as behavioral benchmarks, then the values and norms are cascaded across the entire organization, guiding people in their daily actions, then in this way culture change will be sustained.

Test fields are opportunities like:

- What gets on the calendar?
- What questions are frequently asked? Which ones never?
- What gets followed up? What is forgotten?
- What is important enough to call for a meeting?
- What gets on the agenda? What's on top, what's last?
- In case of conflicting priorities, is Sustainability a guiding criterion for decision-making or do short-term pressures always win?
- What gets celebrated?
- How are social events used? Who gets invited?
- In addition, the shared norms and values can be observed and reinforced during unofficial customs, rituals and by the language used.
- What norms and attitudes are recognized in reward systems? Does it matter *how* business results are achieved or are recognition and performance evaluation only linked to quantitative parameters?

5.5.3 Hard-Wire/Soft-Wire

Creating a Sustainability Culture works on one hand through "hard-wire": Embedding Sustainability related norms and values in all company processes and operations, establishing a clear framework for decision-making and action.

On the other hand, supporting this, "soft-wire" puts the focus on the people processes, ensuring to reinforce Sustainability throughout the entire employee life-cycle (Staffing, Onboarding, Training, Performance Management, Talent Management, Recognition and Reward Systems) and other Human Resources strategies.

Diagnosing culture, establishing norms, values and behavioral attitudes that support a Sustainability Culture, lead to another powerful element of the "soft-wire" approach: establishing competency profiles.

From a clearly articulated strategy (which in some cases may be anchored in aspirational mission statements) and its related company wide, most strategic goals or strategic imperatives it is only a short way to indentifying the most critical competencies required to successfully work on this roadmap.

This process too offers huge opportunities to increase the participation of colleagues, getting their input and at the same time making them messengers for the culture change along the way.

5.5.4 Sustainability as Part of Company Fabric

Once the competency profiles have been implemented, they will serve as key references during many HR processes, putting its stamp on

- Job descriptions
- Job advertisements (internal job posting as well as publicly advertised job offers)
- Recruiting profiles and related interview guides
- Selection criteria
- Onboarding
- Goal setting and Performance Reviews
- Colleague development activities in general and Leadership programs in particular
- Talent profiles and the entire Talent Review process

Thinking from the communication and credibility-building perspective, all the above leads to multiple points of high profile interaction inside the organization as well as with the external community, from search firms to candidates and their environment, to visitors of the homepage and readers of magazines and newspapers.

Since all those interactions will convey a consistent message, in the long run sustainability will become part of the DNA of the company.

5.5.5 Colleague Engagement

When employees realize how they can contribute to the social responsibility of their company during their daily work, they will experience a new level of intrinsic motivation. The linkage between personal beliefs and commitments with the values

of their employer will result in higher employee engagement, since an appreciation of the meaningfulness of the daily job responsibilities is a strong lever, guiding performance as well as employee retention.

Its easy to recognize, that implementing a Sustainability Culture will have significant impact on the way "things get done here", mobilizing all internal and many external resources and expertise.

5.5.6 Feedback Loops

At the same time this wide net of activities will also provide critical checkpoints for feedback, which then drives the necessary fine-tuning of this undertaking.

Going back to the stakeholder approach, here is another example of its application:

- Colleagues will provide feedback during workshops, attitude/colleague engagement surveys, Performance Review discussions and by contributing to existing internal communication processes, placing articles about the experience with the sustainability culture in internal homepages or company newspapers.
- Customers (patients, practitioners, pharmacists) will comment on their satisfaction level and on what changes they observe, same for suppliers.
- Applicants will build their candidature and choice of potential employer on the Sustainability commitment, reading through the job offers, making reference to this during interviews with HR personnel and recruiting managers.
- Search firms can assess the impact of sustainability on the company's image as employer and on its capacity to attract key talent.
- The entire Onboarding process with its many exchanges between the newly hired colleague and various representatives of the new environment will yield a broad range of feedback and comments on how the new culture is perceived.
- NGOs and other watchdog groups[9] will recognize a change towards a more open dialogue, eventually responding with constructive comments about how to enhance the positive impacts of the company's Sustainability efforts. Both sides will gradually quit the "us-versus-them" mindset based on the understanding, that there is nothing wrong with creating societal benefits whilst running a profitable business.

5.6 Going Forward

Having started this review by referring to the current worldwide financial crisis – we may as well end our reflexions there:

---

[9] Various global, cross-industry Collective CSR Leadership Bodies, incl. representatives from the Pharmaceutical Industry are mentioned at: Corporate Leadership Council (February 2006).

It's fair to say, that this crisis will be the acid test for Sustainability Development.

Those who tried to get on the bandwagon of this most needed movement only to fake a positive image will get off right away now since they don't have the proper business rationale to stay in for the long run. The ones operating on solid ground, those who take Sustainability seriously and act as Sustainable Entrepreneurs know why they are engaged in this and so do their employees and other stakeholders. They take this investment as they do with any long-term R&D investment as a means to strengthen the company's future competitiveness.

Interestingly enough though, some valid evidence has already been collected by several institutions and research firms indicating, that those companies with a clear commitment to Sustainability are doing better during this turmoil.

Despite the tremendous damage this crisis causes on individuals as well as on societies around the world, in the end there could also be a positive impact:

As more and more progressive companies across industries, locations and size develop and apply Sustainability practices, those become public knowledge, crafting benchmarks for others and universal standards as well.

Whereas originally for many business leaders Corporate Sustainability seemed to be unthinkable to do, it comes across in the long run as unthinkable not to do.

Bibliography

Barth R, Wolff F (2009) Corporate Social Responsibility in Europe – Rhetoric and Realities. Edward Elgar, Cheltenham Northampton

Bundesministerium für Umwelt Naturschutz und Reaktorsicherheit (BMU) (März 2009) Nachhaltigkeit braucht Führung. Berlin

Collins JC (2004) Good to Great. HarperCollins, New York

Collins JC, Porras JI (1994) Built to Last. HarperCollins, New York

Corporate Leadership Council (February 2006) Driving Social Responsibility through an Organization

Deloitte (27 February 2009) CSR: Sonntagsreden und Unternehmensalltag

Drüner M (March 2009) Steinbeis Hochschule Berlin. Arena for Sustainability

Freeman RE (1984) Strategic management: A Stakeholder approach. Pitman, Boston

Freeman RE, et al. (May–June 2004) Stakeholder theory and "the corporate objective revisited". Organ Sci 15(3)

Glocalist Magazine (November 2008) Nachhaltiges Marketing – mehr als ein Modetrend?

GSK (2005) Corporate Responsibility Report 2005

IBM Institute for Business Value (2008) Attaining sustainable growth through corporate social responsibility. New York

Interbrand Study (September 18 2008) 2008 best global brands. Press release, New York

Kirchhoff (Mai 2008) CSR Kommunikation im MDAX

Leitschuh H (02 April 2009) In der Krise hilft nur Nachhaltiges Wirtschaften. Plattform Nachhaltiges Wirtschaften

Lobby C (November 2007) Greenwash in Zeiten des Klimawandels

Machiavelli N (1985) The Prince. Translated by L.P.S de Alvarez. University of Dallas Press, Dallas

OECD (08 October 2001) Corporate Social Responsibility: Partners for Progress, Paris

Oekom Research (2009) Corporate Responsibility Review, München

Pfeffer J (2009) Shareholders First? Harv Bus Rev 7(8)

Pfizer (2007) Corporate Responsibility Report 2007
Porter ME, Kramer MR (2006) Strategy and society/the link between competitive advantage and CSR. Harv Bus Rev 84(12), 78–92
Raman AP (2009) Emerging strategies to beat the slowdown. Harv Bus Rev 7(8)
Schaltegger S (18 February 2009) From CSR to sustainability. Plattform Nachhaltiges Wirtschaften
Sundaram A, Inkpen A (2004) The corporate objective revisited. Organ Sci 15(3), 350–363
SustainAbility (April 2006) Pharmaceutical Industry Non-Financial Reporting Benchmark. London
The Economist Intelligence Unit (2008) Doing Good: Business and the Sustainability Challenge, New York
Tushman M (2002) Winning Through Innovation. Harvard Business School Publishing, Boston
Umweltdialog (2009) CSR als Wettbewerbsvorteil. CSR_news 2009-04-22
WCED (1987) Development and International Economic Co-operation: Environment, Report of the World Commission of Environment and Development, A/42/427, 4 August 1987. United Nations, Geneva
Weber M (2008) The Business Case for Corporate Societal Engagement. München
Zentrum für Nachhaltige Unternehmensführung (ZNU) (2008) Wittener Impulse – I. Zukunftskonferenz Food. Universität Witten Herdecke

Chapter 6
Reducing the Ecological Footprint of Pharmaceutical Usage: Linkages Between Healthcare Practices and the Environment

Christian G. Daughton and Ilene S. Ruhoy

6.1 Introduction

The design of pharmaceuticals and the practices surrounding the lifecycle of their manufacture and usage are central to minimize their impacts on the environment and increase the sustainability (see Kümmerer, Chaps. 1 and 9, this book) of healthcare. Cradle-to-cradle design, as conceptualized by McDonough and Braungart, could play a key role in redesigning healthcare and reducing its environmental footprint (Daughton 2003). This chapter examines the following thesis involving the environmental sustainability of medication usage: "When actions designed to reduce the potential for environmental impact are integrated within the existing systems of pharmacopeia, pharmacy, and healthcare, significant natural collateral outcomes include improvements in the quality and efficiency of healthcare and in human well-being." The major factors that could shape the future for sustainability of healthcare are discussed.

A confluence of advancements is currently at work in bringing sustainability in quality healthcare closer to reality. These all fall under the umbrella of corporate social responsibility (CSR) and include: information technology, personalized medicine, medical genetics (and epigenetics), green chemistry (e.g., applied to drug design, formulation, manufacturing, and packaging), targeted drug delivery, and the worldwide initiatives called "medications management" and "pharmaceutical care." Together, these areas will largely dictate the shape and size of the environmental footprint for tomorrow's armamentarium of medications.

Without question, pharmaceuticals play extraordinarily important roles in the protection and improvement of human (and animal) health and well-being. Treatment (palliative, symptomatic and sometimes curative) and prevention of disease, together with improved quality of life, are highly visible aspects of a global

C.G. Daughton (✉)
Environmental Chemistry Branch, National Exposure Research Laboratory, US Environmental Protection Agency, Las Vegas, NV 89119, USA
e-mail: Daughton.Christian@epamail.epa.gov

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_6,

industry with predicted sales in 2009 exceeding US$800(BN) (e.g., IMS 2008). The industry's abilities and successes are a testament to over 150 years of innovation and R&D, beginning with the merging of apothecaries with the dye and chemical industry that gradually took place throughout the early to late 1880s and which was later systematized by the efforts of chemists, toxicologists, clinicians, and biologists (Daemmrich and Bowden 2005). Medications are formulated with an array of active pharmaceutical ingredients (APIs) that now total in the thousands and comprise a large number of categories, as shown by the WHO's Anatomical Therapeutic Chemical (ATC) classification system. The ATC system categorizes human APIs across 14 main anatomical groups and then within five different hierarchical levels depending on therapeutic actions, pharmacology, and chemistry (WHO 2008b); an analogous system (the ATCvet) applies to veterinary APIs.

The immeasurable benefits of pharmaceuticals and their ever-evolving sophistication (especially with the application of nanotechnology and biotechnology) are intertwined and tempered by the ever-present possibility of harm – from unexpected or unpredictable adverse reactions (off-target effects), outright toxicity (e.g., from APIs with narrow therapeutic windows, and from cytotoxics in particular), abuse and addiction, and unintentional poisonings (especially for infants, children, the elderly, drug abusers, and pets). Formal systems have evolved worldwide to track these adverse events – the two major ones being poison control centers (WHO 2008a) and a variety of adverse event reporting systems. The latter compose what is generally known as the system of pharmacovigilance, whose formal origin was in France (Daughton and Ruhoy 2008).

The well-known benefits and liabilities of pharmaceuticals are integral to healthcare today, with the practice of medicine having become nearly synonymous with the administration of medications; the imprudent use of medications, however, can lead not just to adverse healthcare outcomes, but also to the potential for adverse environmental impacts. At the same time, other medical and intervention practices that de-emphasize the use of pharmaceuticals, including preventive care as well as palliative care, attract considerably less attention in many countries. The practice of medicine has become very chemical-centric.

Behind the scenes of the extremely visible, prominent roles played by pharmaceuticals in healthcare is another world where pharmaceuticals are involved in a wide spectrum of other, largely hidden and unintended actions – potentially having unanticipated consequences for both human and ecological health. These invisible roles involve a wide array of pathways that lead to unintended (and perhaps unrecognized) exposure and serve to show the interconnectedness of the activities, actions, and behaviors of humans with the environment (Fig. 6.1). In the final analysis, human health and ecological integrity are intimately linked. Actions designed to maintain, alter, or improve human health and well being have consequences for the environment, which in turn can feed back to impact human health – for example by way of recycling ambient environmental residues through drinking water (Daughton 2008).

Drug residues (from both human and veterinary usage) touch the environment in many ways – a reflection of the patient and the environment as an interconnected

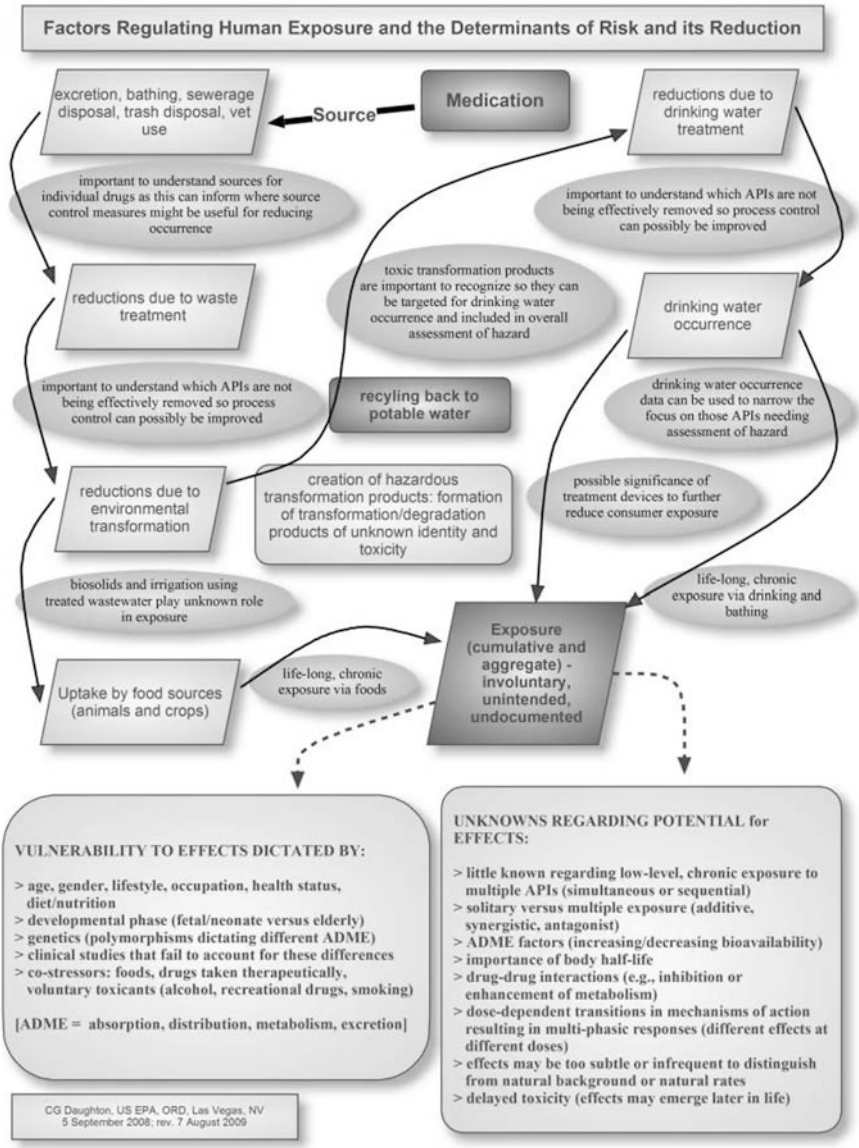


Fig. 6.1 Environmental lifecycle of APIs and human exposure. Points and factors in lifecycle that can be modified to reduce the environmental footprint of APIs

whole (Daughton 2009). They can contaminate: surface and ground waters (via discharge or escape of treated and raw sewage and manure, and disposal of leftover drugs and medicated feeds); arable soils and crops (via use of recycled sewage for irrigation and biosolids for soil amendments); objects that we physically contact (via residues transferred from skin) (Daughton and Ruhoy 2009); sediments (via sorption); and biota (via bioconcentration) (Daughton and Brooks 2011 – tentative). These pathways can all cycle back to human exposure via drinking water and foods (Daughton 2008, 2007).

The mainstream medical literature has only sporadically devoted attention to the fact that drugs persist widely as pollutants in the environment (Daughton 2002, Kuehn 2008, Zuccato et al. 2000). Even the secondary medical literature, primarily journals devoted to pharmacovigilance, had only begun as recently as 2006 to take notice (Daughton and Ruhoy 2008, Kümmerer and Velo 2006, Rahman and Khan 2006). Similarly, the veterinary medical literature began recognizing the issue slightly earlier, with respect to pharmacovigilance (Woodward 2005) and especially the need for better drug disposal (Baird 2003, Crimmins 2001, Haskell et al. 2003, Kuspis and Krenzelok 1996).

The visible and hidden worlds of pharmaceuticals have never been treated together as integral parts of the lifecycle of drugs. Forums to facilitate communication between environmental scientists and healthcare professionals have only begun in the last couple years (e.g., DBU 2008, Keil 2008 – August). The invisible world of pharmaceuticals may need to become a central aspect of healthcare to ensure that the environment is protected. In return, a major unanticipated, collateral benefit could be the optimization of the delivery of healthcare in terms of both therapeutic outcomes and cost (Daughton and Ruhoy 2008). The various roles played by pharmaceuticals in healthcare are currently not in balance with the needs of the ecological environment, nor arguably with the needs of public health and well-being. For example, the WHO notes that proper management of healthcare waste (including disposal of expired pharmaceuticals) is a "public health imperative: that is part of the WHO's core principles for achieving safe and sustainable management of health-care waste" (WHO 2007). Yet there is currently no international consensus – or consensus within the US – regarding the disposal of unwanted medications.

Perhaps the major contributors to the environmental footprint of healthcare are its many inefficiencies and inadequacies. These vulnerabilities tend to promote the otherwise avoidable introduction of APIs to the environment as trace pollutants. The exposure of wildlife and other organisms to these residues holds the potential for a broad spectrum of possible biological effects, but the scope of the potential for impact is only beginning to be extensively explored and documented (see Sumpter, Chap. 2, this book). These residues also experience recycling from surface and ground waters back into the drinking water supply and various foods, where humans of all ages and health status can be chronically exposed to API residues at generally very low levels – but with largely unknown consequences regarding long-term health impacts (Daughton 2008).

Despite the thousands of publications over the last two decades on various aspects of pharmaceuticals as environmental pollutants (US EPA 2008a), it has

only been recently proposed that actions to reduce the environmental impact of pharmaceuticals also can have reciprocal, collateral, positive outcomes for human health – for example, as a result of modified medical practices (e.g., more prudent and appropriate prescribing) and as a result of reduced exposure to environmental residues (Daughton and Ruhoy 2008); also see Götz and Deffner, Chap. 10, this book; Castensson and Ekedahl, Chap. 12, this book. Indeed, possibly missing from green product design and development with respect to sustainable pharmacological care might be a formal evaluation of whether the actions designed to minimize environmental impact have reciprocal benefits for the quality of human health (such as a lower incidence of adverse reactions and improved therapeutic outcomes).

Sweden has been an early pioneer (beginning in the mid 1990s) in attempting to engage the medical community in extending its thinking and practice toward the consequences for the environment – to aim for the practice of ecologically sustainable healthcare. Eckerman and Martineus (1997) presented one of the early discussions targeted to the medical community of the need for medical care that is ecologically sustainable. Early focus was on antibiotic resistance in the environment and on ecologically unsound packaging. But even the more recent examinations of the need for standardized approaches for measuring healthcare waste do not focus on pharmaceutical usage itself as a factor in sustainability (e.g., Tudor 2007).

By implementing any number of a wide array of measures across the many facets of the practice and administration of healthcare, its environmental footprint could be substantially reduced and the overall effectiveness of healthcare could be improved. Of key significance is that a major consequence of any action designed to reduce this footprint is likely to also increase the effectiveness of the practice of healthcare and improve its overall outcomes. If new approaches to medical care were developed that eliminated leftover drugs, for example, the consequent environmental residues would be eliminated, therapeutic outcomes could improve (e.g., because of improved patient compliance and reduction in over-prescribing and inappropriate prescribing), healthcare expenses could go down (e.g., by purchasing only those medications that would be fully consumed), and human morbidity and mortality (due to drug abuse and poisonings from diverted, leftover drugs) could decline. Reducing, minimizing, or eliminating leftover drugs represents a very significant opportunity to improve both ecological and human health and safety.

Over the last century, the direction in which the practice of medicine has been headed holds tremendous promise not just for countless improvements in healthcare, but also for greatly reducing its environmental footprint. Although pharmaceutical usage continues to climb, there has been increasing attention to a new direction in shifting away from treating illness once it is manifest and instead toward a focus on prevention and wellness. The shift began to be formalized in the US in 1948 with establishment of the American Board of Preventive Medicine and Public Health (which shortened its name in 1952 to the American Board of Preventive Medicine – ABPM). Facilitating this is the emergence and convergence of personalized medicine and medical genetics/epigenetics, as well as advanced informatics and other information technology. This paradigm shift has been made possible primarily by advancement in understanding the human genome (and biomarkers

based on the many other "omics" subdisciplines, such as proteomics, metabolomics, and glycomics) and by advancements in analytical chemistry, computer technology, and bioinformatics, required to handle the voluminous, complex, rich array of data generated by the omics fields.

6.2 Improving the Efficiency of Pharmacy

6.2.1 Mining of Healthcare Data

Health information distribution organizations purchase prescription records and then mine, aggregate, and sell detailed data and derived statistics regarding drug sales. The largest of these is IMS Health; others include Verispan, Dendrite International, and Wolters Kluwer. IMS Health, for example, mines monthly data from nearly 1 billion prescription sales (comprising 75% of all drug sales) involving over a million products from over 3,000 manufacturers in roughly 100 countries. At the same time, pharmacovigilance programs track adverse events linked to individual drugs. Noteworthy here is the redesign of the US FDA's Adverse Event Reporting System (AERS) under the "Sentinel Initiative" (initiated in May 2008), whose objective is to create an integrated, electronic system for the nationwide monitoring of medical product safety (US FDA 2008b).

Even though these extremely detailed data are available from drug sales and pharmacovigilance programs, comparatively little is known regarding what percentage of each drug sold is actually ever consumed, or moreover, whether the drug was even effective in achieving its intended effect (such as symptom relief) or outcome (e.g., curing of disease or resolution of condition). Also not tracked is the incidence of absence of measurable or detectable outcomes, which can indicate when a medication was needlessly administered. The practice of pharmacovigilance is currently designed to accomplish only half of the job (determining which drugs pose risks), while those drugs that are ineffective continue to be prescribed. These deficiencies, in what should be a continuum of healthcare, contribute to unneeded excretion of APIs and accumulation of leftovers eventually necessitating disposal (especially from drugs that are needlessly administered) – both being major contributors to the entry of APIs into the ambient environment. Clearly, a comprehensive database of patient outcomes (both adverse effects and ineffective outcomes) from medication could prove extremely useful for improving the efficacy and efficiency of future prescribing practices.

The evolution of the practice of medicine has progressed faster in the delivery of healthcare than in achieving outcomes (e.g., life expectancy and quality of life). Advancements in more tightly integrating these two into a more efficient healthcare continuum could serve as a major catalyst in reducing the prescribing of medications that are ineffective for specific patients or situations or of inappropriate doses or durations.

Careful examination of all the aspects of a healthcare program is needed to ensure quality. The so-called "program logic model" provides a systematic approach for ensuring continual improvement of any complex system by merging into a continuum the often isolated steps of planning, implementing, evaluating, and communicating (e.g., see discussions by Daughton 2004, Joly et al. 2007); this continuum links inputs (resources and investments), outputs (accomplishments and products), and outcomes (ultimate impacts and significance).

While these deficiencies persist, could existing data in the interim be used to answer some key questions, such as the degree to which a medication is fully consumed or left over? Some of the many possible uses of existing data include: Do short-term refills of maintenance medications likely indicate fewer leftovers as a fraction of the total used during the course of treatment? Conversely, do auto-refills indicate a high probability of leftovers? Do scripts for a full course of treatment (and especially a 90-day immediate supply) in the absence of a trial course indicate a high probability of leftovers? Is unintended, unrecognized polypharmacy occurring? Could ready access to a comprehensive prescription history avoid the prescribing of medications already used by a patient in the past but which proved ineffective and was forgotten as so by the patient? Many of these gaps in our knowledge of the lifecycle of medications could be eliminated with the eventual fruition of personalized medicine (see below), especially the use of centralized electronic health records.

Large differences are known to exist in sales of drugs between geographic locales (Ekedahl 2002). This information can be mined to address any number of healthcare questions, for example: to assess the impact of public guidance, regulation, and policy on medication use; improper, inappropriate prescribing and abuse; and adverse drugs reactions (ADRs). Better data for these factors could play key roles in improving the sustainability of healthcare. Even more value could be derived by interfacing these existing databases with geographic information systems containing API environmental monitoring data.

6.2.2 Electronic Systems

Medicine has been increasingly adopting digital technologies, such as e-prescribing (including e-sampling), electronic health records, and electronic decision support systems (e.g., for ensuring quality control for drugs subject to restricted access prescribing). Information technology will play a central role in the modernization of medical care. Digital systems will vastly improve the quality and timeliness of prescribing and dispensing, and also facilitate the consumer in assuming more control over their own healthcare information.

The early stages of digital solutions targeted for the consumer range from those that are publically accessible, such as Microsoft's HealthVault (http://www.healthvault.com/) and Google Health (www.google.com/health) to those implemented by the healthcare industry, such as the pioneering program of the Cleveland Clinic: *MyChart* (http://eclevelandclinic.com/cms/mychart.html),

and e-prescribing as facilitated under the Nationwide Health Information Network (NHIN) (see discussion below); systems that aggregate data across disparate systems [such as *Amalga* (Microsoft 2009)] are key to providing healthcare professionals with a unified, common view of patient histories and needs. After all, most patient medical information is currently not digitized and therefore provides limited value to physicians, pharmacists, or patients themselves.

Ready access to comprehensive and accurate medical information could address many of the problems that lead to leftover medications and medication overuse; unintended polypharmacy (Gorard 2006) is one example (see Fig. 2 "Factors Influencing Drug Consumption" in: Ruhoy and Daughton 2008).

Finally, harmonized and widely promulgated approaches are needed for drug disposal, unused drug collection take-backs, recycling (permitting exchange or redispensing of unused drugs under controlled conditions or among countries), evidence-based prescribing, pharmacovigilance, charitable contributions, and monitoring/tracking of API residues in the environment and foods. One such proposal is a global pharmacogenomics network, specifically to study severe adverse drugs reactions (Giacomini et al. 2007). Another example is the International HapMap Consortium, which coordinates information about the identification of single-nucleotide polymorphisms (SNPs) associated with human disease and the correlations of these with pharmaceuticals (HapMap 2008). The mining of comprehensive drug usage data from inventories of unused drug collections holds the potential to provide invaluable insights regarding prescribing and dispensing habits, revealing aspects that could be improved to reduce the incidence and magnitude of leftovers (Ruhoy and Daughton 2008). Leftover drugs are diagnostic of something amiss in the prescribing/dispensing system; an extreme example is the magnitude of wastage that can occur as a result of drug contributions during humanitarian crises (e.g., Pinheiro 2008, WHO 1999).

6.3 Personalized Medicine – A Framework for a Sustainable Pharmacy

Looking toward the future, what developments or trends might have the largest impact on increasing or reducing the footprint of healthcare? The many factors that influence the use and over-use or misuse of medications and which subsequently lead to their accumulation and need for disposal are well-documented (see: Ruhoy and Daughton 2008, and references cited therein). These factors figure prominently in the environmental footprint of pharmaceuticals. To address this most directly, consider the ramifications of a fully developed, integrated approach to personalized medicine (PM). Probably no other single development holds the potential for more profoundly optimizing the use of drugs and reducing unneeded usage.

Personalized medicine, in its current form, is a relatively new paradigm in the practice of medicine. It will likely serve as the organizing framework around which a revolution in the usage of APIs will occur, probably leading to profound changes in

the types (e.g., for orphan diseases) and quantities of APIs introduced to the environment. Many advances in healthcare that lead to improved therapeutic outcomes will also result in reduced usage of medication. Widespread implementation of advanced forms of PM could lead to the usage of a wider spectrum of drug classes, especially many new specialized classes. It could also lead to an increased usage of certain individual APIs. At the same time, however, PM could also result in lower usage of most APIs as a result of their being targeted solely for use in situations where the probability of efficacy is very high and being prescribed in personalized dosages. Reduced costs in drug development and clinical trials (guided by PM) could lead to lower prices, thereby affording wider usage of drugs among responder populations and greatly reduced usage among non-responders.

In the early 1990s, PM referred to the rather general and vague notion of a patient-centered practice of medicine. The idea developed momentum in the late 1990s with the advancement of the Human Genome Project (Adam et al. 1999). It has since developed more concrete, specialized embodiments. The journal *Personalized Medicine* was launched just in 2004. The Personalized Medicine Coalition (PMC) was founded in 2003 (http://www.personalizedmedicinecoalition.org), and the Partnership for Personalized Medicine was formed in 2007. Several terms have evolved to describe various dimensions of PM, including: pharmacogenomics (PGx), targeted medicine, predictive medicine, smart medicine, rational drug therapy (Ekedahl 2002), precision medicine, evidence-based medicine, outcomes-based medicine (vs. symptom-based), tailor-made medicine, stratified medicine (Trusheim et al. 2007), and customized care; the Institute of Medicine has described a process for mining and objectively evaluating evidence (IOM 2008). These contrast sharply with the empirical process (Trusheim et al. 2007) currently used in prescribing (in those situations when the risk of serious side effects is low), which often entails trial and error in drug selection, dosing schedule, duration, and dosage – often being "one-size fits-all." This conventional approach is noted in the US for playing a role in the annual prescribing of roughly 3 million incorrect or ineffective drug prescriptions, with outcomes sometimes similar to those of outright prescribing/dispensing errors (SACGHS May 2008). This empirical approach to prescribing, with its many limitations, has led to the advent in Europe of pay-for-performance pricing (cost-justified payment systems) for pharmaceutical treatment (Pollack 2007).

A concept called chemical management service (CMS), part of the larger concept of "material flow management service," strives to sell the service or outcome intended to be accomplished by use of a chemical, rather than selling the chemical itself (Stoughton and Votta 2003); an example of a formalized CMS is "chemical leasing" or ChL (UNIDO 2008). Applying the concept of CMS to healthcare, an ultimate objective could be the paradigm whereby medications are no longer sold or prescribed by themselves, but rather the desired therapeutic, lifestyle, or enhancement endpoint becomes the actual contract with the patient.

The ultimate hypothetical objective of PM is to aim for the optimal therapeutic response for a particular condition in a specific patient. This is achieved in a specific patient by selecting the optimal drug combined with the optimal dosage and

dosing schedule (e.g., times of the day or coordination with physiological rhythms) and for the optimal duration, while minimizing side-effects. At the same time, PM would be used to actively avoid the use of medications for individuals with a contraindicated predisposition. For this reason, older drugs having a wide spectrum of side effects could possibly again prove useful in targeted sub-populations where these effects are muted. Currently these drugs are often used only in severe medical scenarios when all other therapeutic options have been exhausted. PM could also facilitate earlier diagnosis and treatment, possibly permitting less sustained pharmacologic interventions. It can also be used for screening, which is used to determine the predisposition for future disease with the use of prognostic tools in order to custom-tailor preventive measures.

Even the drugs used most widely – the "blockbuster drugs" – typically show efficacy in only 40–60% of patients (PricewaterhouseCoopers 2005). In a well-publicized remark, Allen Roses, a vice-president of GlaxoSmithKline, stated that "the vast majority of drugs – more than 90% – only work in 30 or 50% of the people" (Connor 2003). This means that for roughly the majority of usage, drugs are being used inefficiently at best or inappropriately or imprudently at worst. Such non-targeted usage, in turn, can promote the need for auxiliary medications to counteract side effects as well as additional medications to further assist in treatment of the original symptoms. If the majority of drug usage is unwarranted, this leads to gross over-usage and accumulation of leftover drugs from non-compliant patients, who often comprise the poor-responders and non-responders. This excessive use then results in the unwarranted introduction of APIs to the environment, from sources that could have been avoided – excretion, bathing, and disposal.

Poor metabolizers can also contribute a disproportionate fraction of parent API to sewage via excretion. PM could radically reduce or eliminate the unnecessary use of drugs in these instances (by roughly half). Poor patient compliance with medication regimens is a major cause of accumulation of leftover drugs (BCG December 2003, Ruhoy and Daughton 2008). Over the last 20 years, fatal poisonings from domestic medication errors have increased dramatically (Phillips et al. 2008). These include deaths resulting from unintentional poisonings (e.g., overdose), from use of the wrong drug (e.g., medication taken by someone for whom it was not intended), and drug-drug interactions (made worse by polypharmacy). An unknown portion of these fatalities is a consequence of leftover medications that are inappropriately stored in the home instead of being properly disposed (Daughton and Ruhoy 2008, Ruhoy and Daughton 2008). Improved compliance and less wastage could result from increased trust or certainty by the patient in the efficacy of drugs.

6.4 Pharmacogenomics (PGx)

A prime objective of personalized medicine is to take into account the many differences between individuals and how these variables interact. Differences include genetics (such as slow and fast metabolizers and non-responders), epigenetics,

gender, age, ethnicity, health status, idiosyncrasies in chronobiology (Smolensky and Peppas 2007), response to diet, exercise, and environmental, chemical or other stresses. The interplay between the environment and gene expression is known as "ecogenetics" (Costa and Eaton 2005) and shows how changes in an individual's lifestyle, diet, high-risk behaviors, and so on could be as important as medications. Even the microbial communities of the intestinal tract, which vary greatly among individuals, can dictate responses to drugs. Acetaminophen (paracetamol) liver toxicity, for example, is partly determined by competitive inhibition of its detoxication via O-sulfonation by microbial production of p-cresol (Clayton et al. 2009). Important to note is that improvements in analytical capabilities for elucidating genetic factors will provide a dual-sided tool. Identifying genetic susceptibilities to medication will not only improve the efficacy of healthcare, it will also provide better insights into vulnerable subpopulations required for environmental risk assessments from chemical exposures in general.

Genetic polymorphisms in part dictate some of the potential for developing a health condition. At the same time, they allow for opportunities to better target treatment. After all, the need to remove certain drugs from the market is sometimes simply the result of genetic and epigenetic anomalies among small sub-groups that respond adversely. Screening tests designed to identify these sub-groups that do not respond properly to a drug can be used to "rescue" a drug from failure during clinical trials and to attain regulatory approval. In addition, those with particular polymorphisms of disease can be treated with different regimens than others with a similar diagnosis (e.g., hormone-responsive cancers). The important role played by chronobiology (Smolensky and Peppas 2007) with regard to the timing of drug delivery is exemplary of the many factors that have yet to be widely implemented in personalized medicine. The delivery of a medication timed according to natural rhythms not only can lessen the incidence of adverse reactions, as with chemotherapy, but in some instances it also allows for lower (or higher but less frequent) doses. Timing of a dose can affect both pharmacokinetics and pharmacodynamics. As personalized medicine develops, more specialized segments of pharmacotherapy, such as chronotherapeutics, will emerge as common modes of therapy.

For a truly sustainable pharmaceutical treatment model, considerations for environmental impact would need to be incorporated – to minimize excretion of bioactive parent APIs or metabolites (including conjugates subject to "reversible metabolism" [or "futile cycling"] back to the parent aglycone) and minimize leftover medications that would otherwise require disposal. Probably the first formalized program to begin taking some of these many factors into consideration was the environmental classification system introduced in 2003 and further refined by the Stockholm County Council (2008); also see Wenmalm and Gunnarsson, Chap. 16, this book.

Inefficiencies in medical prescribing and in dispensing often translate directly into added impacts on the environment. The costs of suboptimal drug therapy primarily revolve around drug-induced morbidity and mortality and poor response to treatment. By reducing the incidence of sub-optimal therapy, not only would health

outcomes vastly improve and patient expense diminish, but drug use in many cases could be reduced, thereby leading to lower potential for impact on the environment.

Roughly, only 10% of all new molecular entities (NMEs) ever gain approval and commercialization, largely as a result of unforeseen adverse reactions or lack of response in large, untargeted populations. Of the drugs that fail during development, 58% have been found to be terminated because of efficacy or safety concerns. Nearly 79% of investigational new drugs fail during clinical development (PricewaterhouseCoopers 2005). This extremely costly step could be vastly improved with advancements in pharmacogenomics (and proteomics and epigenomics).

Numerous studies have verified the large role that medications play in morbidity and mortality. A study at a Canadian hospital revealed that of the adults presenting at an emergency room, 12% were drug related, and, of these, nearly 75% were deemed of moderate severity and nearly 10% as severe (Zed et al. 2008). The causes were classified as adverse reactions (39.3%), non-adherence (27.9%), and use of the incorrect or suboptimal drug (11.5%). Clearly, improvements in the realm of drug prescribing (e.g., via PM), dispensing, and patient education (e.g., via implementation of "pharmaceutical care" programs, see below) hold the potential for reducing adverse events and improving therapeutic outcomes. So do dispensing and patient education, for example via implementation of pharmaceutical care programs. This could also reduce the use of medication in certain instances and lead to reduced environmental loadings of APIs via excretion or disposal.

Pharmacogenomics can define new uses or targets for existing or old drugs. It could also increase the approval rate of NMEs, which have composed a minority of new drug approvals in the US (PricewaterhouseCoopers 2005). Pharmacogenomics could reduce the size and duration of clinical trials via narrower stratification, as the discriminatory power would be vastly improved as a result of eliminating non-responders. This would yet further increase the approval rate of NMEs. While concentrations of individual APIs in the environment might go down, the increased numbers of new APIs could possibly complicate the assessment of risk for the environment. Likewise, as new therapeutic molecular targets are revealed, new uses will emerge, leading to yet more NMEs.

In the US, the number of NMEs withdrawn from the market for safety reasons over the last 3 decades has totaled about two dozen, and represented roughly 3% of the total NMEs approved (Anonymous 2008, Kaitin 2005). With tests that could reveal the stratified populations for which these NMEs (and those with box warnings) would result in adverse reactions, these NMEs could possibly be reintroduced or used with vastly improved safety with relabeling.

Development of test procedures (known as diagnostic-therapeutic tandems, companion diagnostics, "theranostics," or pharmacodiagnostics) to target the appropriate sub-populations could greatly increase the approval rate for drugs while vastly improving their efficacy (in the target population). The potential for increasing the apparent effectiveness of a drug could theoretically approach 100%. The integration of pharmacogenomics with companion diagnostics to accurately target the selection of optimal drugs and their dosages, and the optimal duration of therapy,

results in what are known as drug/test combination products (Warner 2004); the first combination product, approved in 1998 by the FDA (HercepTest/Herceptin), was for HER2-positive breast cancer; the diagnosis of HER2-positive breast cancer itself is a result of medical genetic testing. Pharmacogenomic information (specifically genomic biomarkers) useful in selecting appropriate medications for individual patients is increasingly being included with approved drugs; see the list maintained by the US FDA (US FDA 2008a).

6.5 Outlook for Personalized Medicine – Extending the Focus from Treating Symptoms to Achieving Efficacious Therapeutic Outcomes

The advent of mainstream PM and its many innovations will pose major challenges for a wide range of stakeholders, all of whom will need to begin working closely to coordinate their efforts. Ethical and public concerns will demand careful attention – not just secured protection of personal information by healthcare professionals, clinical researchers, and the health insurance industry, but also selection or exclusion of participants for clinical trials and appropriate approvals by an institutional review board (independent ethics committee or ethical review board).

Perhaps the major obstacle to developing and implementing advanced genetic testing is the safeguarding of personal information from misuse by employers and health insurers. Vulnerabilities in ensuring privacy have even created roadblocks for clinical research on genetic testing because of the privacy concerns held by potential recruits. Strict regulations will be needed to guarantee the privacy of genetic information (especially genetic exceptionalities) in order to prevent discrimination. One example, in the US, is the Genetic Information Nondiscrimination Act (GINA) of 2008 (Hudson et al. 2008). Some of the quandaries posed by genetic testing are discussed by Korobkin and Rajkumar (2008).

Continual advancements will also be needed in medicinal analytical chemistry and biology for techniques that are sensitive, specific, and accurate for clinical use and which can broaden the scope of "omics" targets needed for fast and inexpensive tests for diagnosis, prevention, and prognosis. Rapid, inexpensive, standardized, valid tests with unequivocal results are also needed to make in-treatment monitoring more accessible to patients, thereby promoting proper decisions on the need for treatment, avoiding over-treatment, and ensuring proper dosage or biomarker titers. Of equal importance is that the tests need to have clinical utility – the results need to potentiate outcome-oriented actions on the part of the physician and patient. Over 1,500 medical conditions can now be revealed by genetic testing. While their current usefulness or efficacy is open to debate, personal genetic testing became readily available directly to the consumer in 2007 – tests primarily using DNA chips that can reveal thousands of SNPs; the first available were *23andme* (https://www.23andme.com/) and *deCodeMe* (http://www.decodeme.com/), followed by a service offered by Navigenics (http://www.navigenics.com/).

Drugs with better patient targeting may not require the broad-based direct-to-consumer (DTC) advertising campaigns that have been such an integral part of the blockbuster drug paradigm in the US and New Zealand. Targeted medicine could negate the usefulness of DTC advertising and thereby reduce the imprudent use of medications by those who would not benefit. The need to "invent" new diseases or conditions, in order to expand markets for existing medications, would perhaps lessen, as the numbers of actual, identifiable disease targets would increase. Another aspect of PGx drugs might also be beneficial for the environment. These drugs will undoubtedly command higher prices (because of their known, proven efficacy) and therefore will less likely be over-prescribed by the physician or to be under-used by the patient.

Of course, establishing a higher rate of patient trust in medications with assurances that medications will have the intended (therapeutic or cosmetic) effects while avoiding side effects could be a major objective of PM; equally important would be verification when treatment is unnecessary. But a larger challenge will be to establish stronger linkages between therapeutic effects (for example, lowering cholesterol) and actual, positive therapeutic outcomes (for this example, reduced cardiovascular disease). This step would yet further reduce the use of drugs that happen to be efficacious in treating symptoms but not in attaining significant outcomes (e.g., longer survival, higher quality of life, etc.). PGx holds the potential to treat with a focus toward therapeutic outcomes rather than symptoms. The prospects of attaining curative treatments could reduce the need for certain long-term maintenance medications, which can be a major source of continual input to the environment via excretion or by way of disposal. Earlier detection of disease (especially cancer) with better diagnostics could also obviate the need for longer-term and maintenance therapies – even more so if actual cures can be developed. Perhaps offsetting this reduced source for entry to the environment, however, might be the development of APIs that can change fatal diseases into chronic conditions that might require indefinite treatment with other APIs. Overviews of these aspects of PM and many others involving its advancement, acceptance, and broad implementation are available from Eckerman and Martineus (1997), SACGHS (May 2008), and Katsanis et al. (2008).

Clearly, personalized medicine has great potential for altering the usage of pharmaceuticals, in terms of both the quantities and types of APIs. PM therefore has the potential for indirectly and passively reducing environmental impacts of APIs by simply reducing their initial entry to the environment. More direct and active intervention in reducing environmental impact can be taken by addressing the many factors that dictate the environmental footprint of an API, beginning with the drug development process itself (see Taylor, Chap. 7, this book; Kümmerer, Chaps. 1 and 9, this book). Drug development is driven not just by measures of efficacy and safety, but also by factors only tangentially related to patient use or benefit, such as drug and target discovery, drug design and formulation, synthesis, production, manufacture, packaging, and marketing; the size of potential markets in another factor, resulting in few pharmaceuticals for orphan diseases. The long and

complex decision process required for determining whether to proceed with commercializing a drug could be augmented with the factors that dictate environmental impact, including persistence and potential for bioconcentration (e.g., Gunnarsson and Wennmalm 2008, Wenmalm and Gunnarsson, Chap. 16, this book; Stockholm City Council 2008) as well as pharmacokinetics contributing to extensive excretion (or conjugation) or pharmacodynamics involving receptors in non-target species. Candidate APIs that have undergone and passed screening for environmental impact may also have a higher probability of passing clinical trials, simply because they may necessarily have a lower incidence of adverse effects.

Even more value could accrue by integrating the concept of *pharmEcovigilance* (discussed below; Daughton and Ruhoy 2008) with a synthesis of other technologies. As an example, by integrating near real-time prescribing/dispensing data, adverse event reporting, and environmental monitoring of APIs, into a geographic information systems platform, a broad spectrum of insights could be rapidly acquired, especially with regard to status and trends of API pollution on local scales, or even the emergence of new disease trends.

At the same time, certain emerging trends hold the potential to greatly increase the use of some medications. A case in point has been the efforts in the US to switch certain statin medications from prescription-only status to over-the-counter (or behind-the-counter), which could lead to the long-term self-management use of this class of drugs by many who would ordinarily not be candidates for treatment (Tinetti 2008). Long-term self-medication is particularly problematic for conditions that are asymptomatic such as hypercholesterolemia, where periodic testing is required to gauge status, and is also problematic for treatments that should be monitored in terms of potential unwanted effects. An example of the latter is patients who are taking certain statins, who need biannual liver function tests. Working in the background against evidence-based medicine is a wide spectrum of programs and activities designed to increase sales of medications through increased script writing. One example is the use of influential physicians known as "key opinion leaders" to make paid presentations to groups of physicians (e.g., see: Moynihan 2008). By making these programs completely transparent, others would be better able to make more informed judgments as to the veracity and accuracy of claims. Another trend away from transparency is ghostwriting and pseudo journals (Fugh-Berman 2009, Sismondo 2007).

Finally, counterfeit drugs – those with alternative, undeclared active ingredients – serve to contribute to the numbers of different APIs in the environment. Many of these APIs are new "designer" drugs – some with chemical structures that have yet to be elucidated. Among the adulterants sometimes added to herbal supplements or that serve as the undeclared active ingredients in counterfeit OTC/Rx drugs (often at very high levels) are a number of previously unknown analogs of the approved phosphodiesterase type 5 (PDE-5) inhibitors, which include sildenafil, vardenafil, and tadalafil (Venhuis et al. 2007). This trend further complicates development of a comprehensive assessment of API occurrence in the environment.

6.6 Improving Drug Delivery and Chemistry by Design

In the US, the Pollution Prevention Act of 1990 encouraged the US EPA to pursue alternative pathways for chemical synthesis in line with "reducing or eliminating the use or generation of hazardous substances during the design, manufacture, and use of chemical products and processes" (US EPA 2008b). In 1993, this approach was formalized as the Green Chemistry Program. The idea that "benign by design" could at the same time lead to products with improved performance characteristics followed years later.

Green chemistry will play a central role in reducing the environmental footprint of APIs and in striving to make drug-based medical care more sustainable. Opportunities for the application of green chemistry span the spectrum from drug design, formulation, delivery, and packaging, to waste treatment (see Kümmerer, Chaps. 1 and 9, this book; Taylor, Chap. 7, this book). Progress in any of the following, for example, serves to reduce the footprint of APIs: (i) streamlining drug discovery [e.g., capitalizing on ethnobiology, which in turn can catalyze the protection of endangered geographic locales (e.g., Mihelcic et al. 2007)]; (ii) synthetic routes that rely less on hazardous reactants, reduce production of hazardous waste, or lower energy consumption, such as use of biocatalysis (Woodley 2008); (iii) optically pure APIs (eliminates non-therapeutic chiral isomers and reduces overall dose) (Daughton 2003); (iv) isotopic substitution to make deuterated analogs of APIs can alter pharmacokinetics/pharmacodynamics because of the kinetic isotope effect (Sanderson 2009); this can yield drugs with greater stability, facilitating longer half-lives (increased duration of action from hindered first-pass metabolism), and result in fewer side effects because of lower doses; (v) chemical structures more amenable to microbial and chemical structural transformation or degradation, which lead to shorter environmental half lives and reduced potential for bioconcentration in non-target organisms (Daughton 2003, Daughton and Brooks 2011 – tentative; Kümmerer 2007), and structural transformation to more innocuous end products; (vi) structures, formulations, or delivery devices that facilitate the API to selectively reach its biological target (thereby reducing dosage); (vii) the use of multi-API therapies to lower the dose of each individual API while also resurrecting APIs that have dropped from use because of failing efficacy, such as development of microbial or tumor resistance (combination high-throughput screening approaches can now rapidly locate APIs that can work together synergistically) (Borisy et al. 2003, Mayer and Janoff 2007); (viii) packaging that promotes longer shelf life or provides accurate real-time indication of expiry status (e.g., Galagan and Su 2008), reducing the need for disposal [especially important for those drugs sensitive to light, moisture, or oxygen (e.g., Rosenberg et al. 2008)]; and (ix) low-cost, benign destructive waste treatment approaches that can be adopted by existing waste and drinking water treatment facilities or even by healthcare/consumers.

Drug packaging alone can play a large role in leading to the need to dispose of drugs. Possible improvements include reinventing to enhance security (e.g., ensuring tamper proofing is one limitation to drug recycling), providing visual confirmation of whether a medication has reached expiry prematurely (e.g., because of

storage in excessive heat or humidity) or if it has not truly become unusable by the label date, and developing easy means of testing actual shelf life [some drugs can have shelf lives that far exceed the default 1 year (e.g., see: Daughton 2003)]. These improvements might greatly facilitate the safe reuse of previously dispensed medications or the sustained use of medications erroneously thought to have expired. The composition and physical design of packaging itself could also be optimized to reduce its own environmental footprint (especially reducing resources required for manufacture and wastes created during disposal). Packages with reduced numbers of doses or extended shelf-lives could also steer consumers away from purchasing supplies that are not possible to fully consume prior to expiration (Daughton 2003).

Bewildering spectrums of approaches have been developed or are under development for better-targeted delivery of APIs. By making delivery to the target site more precise and efficient, doses can be vastly reduced while greatly minimizing or eliminating side effects caused by systemic release; one of many examples is the technology for creating antibody-drug conjugates linking ultrapotent cytotoxics with antibodies targeted for receptors such as those on tumor cells (Thayer 2008). With such specificity in targeting, APIs that ordinarily would be too potent could theoretically be used safely, while greatly reducing side effects. Note that sometimes doses could be reduced solely because the clinical trials had been designed with the maximum tolerated dose (to ensure statistically significant outcomes). The armamentarium of effective APIs could also be greatly expanded by making use of those existing APIs having high biological activity but which otherwise cannot reach their targets (for example, cellular uptake is nil because of biophysical barriers). A case in point is the polyphenol present in green tea (epigallocatechin-3-gallate – EGCG), which has very high anti-tumor activity but therapeutic levels cannot ordinarily be achieved in tumor cells (Siddiqui et al. 2009). Nanotechnology might play an important role in advancing the effectiveness of new delivery approaches (dosage forms and platforms). Advances in expanding the dosage forms of biologicals (especially oral dosing) could have considerable implications in reducing the use of conventional small-molecule synthetics. Timing of dose can sometimes be as important as physical targeting of dose. An example is specially formulated chronotherapeutics designed to release APIs timed to the proper periodicities of rhythms (Smolensky and Peppas 2007).

On the down side with respect to potential environmental impact, improved delivery could facilitate the increased use of ultrapotent APIs, which could counterbalance any environmental gains from reduced dose; the ratio of the environmental concentration resulting from the quantity consumed to the thresholds of toxicological concern are not radically altered. While an ultrapotent API would reduce its overall mass loading in the environment (from excretion or bathing), the greatly increased potency of the API may serve to re-adjust the potential for its effects in the environment. Another example is a new class of radiopaque iodinated polymers that are biodegradable, as opposed to those iodinated X-ray contrast agents that are currently widely used and quite persistent (Carbone et al. 2008).

Another example of how improved delivery technology could reduce the environmental footprint of APIs is the continued, increasing development of natural

peptides and modified proteinaceous APIs, as well as other approaches such as those based on oligonucleotides (e.g., miRNA) or their antagonists (termed "antagomirs") (e.g., see: Krutzfeldt et al. 2005). The expanding role of biotechnology in drug design could have major ramifications for environmental impact. Natural peptide and modified proteinaceous APIs continue to experience increased development as drugs (insulin still being the most widely known, having been introduced to clinical practice in 1921). The major weakness of these molecules for therapeutic use by oral delivery is their comparative fragility, being vulnerable to degradation by proteolytic enzymes or structural denaturing in the gut, and poor bioavailability from the gut. Major advances in formulation and delivery technology are serving to protect these APIs from degradation/denaturation in the gut and improve uptake; this could facilitate greatly expanded acceptance in healthcare (Levy 2008). While attracting little attention by environmental scientists, this broad class of APIs will probably have a considerably smaller environmental footprint than the more structurally stable synthetic APIs. Those that do get excreted – and even if surviving sewage treatment and environmental transformation or denaturing – would probably have considerably lower potential for resulting in exposure of non-target organisms because of their poor absorption across the skin or via the gut and propensity for environmental degradation or denaturing by microorganisms, sunlight, and other physicochemical processes (see Straub, Chap. 8, this book; Kümmerer, Chaps. 1 and 9, this book).

Overviews and discussions of life-cycle considerations and green chemistry relevant to reducing the footprint of APIs are covered by Clark et al. (2007), Constable et al. (2007), Fichana (2005), Gunnarsson and Wennmalm (2008), Henderson et al. (2008), Khetan and Collins (2007), (Kümmerer 2007), and Tucker (2006), among others.

6.7 "Pharmaceutical Care": An Avenue to Improved Health Care and Reduced Environmental Footprint

The practice of pharmacy has progressed through many phases over the centuries, reflecting periodic restrictions and expansions in the roles played by pharmacists in their relationship with patients. The most recent phase has expanded the role of pharmacists under a concept called "pharmaceutical care," which has been merging with an allied concept called "medications management" (Bajcar et al. 2005, Woodend 2003). With its origins beginning in the 1970s, a widely accepted definition of pharmaceutical care was published by Hepler and Strand (1990) as: "pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life." The formal concept of pharmaceutical care has different meanings in different countries. The history, evolution, and wide diversity of approaches in its implementation among countries have been covered in many publications over the last few decades; some of the more recent examples include: Berenguer et al. (2004), Martin-Calero et al. (2004), Pearson (2007), and van Mil et al. (2004).

The ways in which pharmacy is practiced clearly have ramifications for environmental impact. The actual practice of pharmaceutical care is implemented with various degrees of autonomy for the pharmacist and degrees of involvement with the physician – ranging among supplemental, collaborative, and independent models of prescribing (Pearson 2007). Although pharmacy systems differ widely around the world, prescribing authority has been extended in various degrees to nurse practitioners, physician assistants, and pharmacists, with the ultimate implementation being the empowering of pharmacists to act as prime prescribers rather than just dispensers (with internal controls preventing a pharmacist from both prescribing and dispensing for a given client/patient, in order to avoid conflicts of interest). In effect, this evolutionary step is transforming pharmacy from a customer-oriented practice to one focused on patient care. This step takes pharmacy beyond the sole focus of dispensing medications to the value-added dispensing of knowledge, all of which require more focus on continued education and training and elevated responsibilities.

Healthcare will probably see a continued evolution toward closer working relationships between pharmacists and physicians. Many different models of practice will undoubtedly emerge, involving an array of physician/pharmacist collaborations or partnerships, where pharmacists could eventually become pharmacotherapy experts working as integral parts of medical practices (see: White and Latif 2006). Indeed, hospital care teams usually consist of a pharmacist with the sole purpose of consultation on treatment implementation and monitoring of hospitalized patients. The traditional role of dispensing could transition away from pharmacists, toward pharmacy technicians, using increasingly more sophisticated automation and computerized knowledge systems. Dispensing could be more tightly regulated with respect to quality control, one obvious outcome being to greatly minimize dispensing errors (and thereby help to reduce the incidence of unused drugs). By linking such systems with real-time databases for adverse drugs reactions and with information needed for personalized medicine, the possibility of inappropriate prescribing, unessential prescribing (e.g., human "enhancement"), and unnecessary dispensing could be greatly reduced; the ready detection of unnecessary or dangerous polypharmacy for individual patients being treated by multiple physicians (often without each other's knowledge) is one of many examples.

Portions of such an electronic framework are emerging in the US in the form of e-prescribing, as facilitated by the Nationwide Health Information Network (NHIN) under the US Department of Health & Human Services (HHS 2009) and as the e-prescribing network operated by Surescripts (Surescripts 2009); as a pioneering venture in e-prescribing, Surescripts is the largest commercial, real-time, nationwide prescribing and information exchange network, which in part provides a patient's medication history and decision support tools for physicians. In-depth perspectives on electronic connectivity in healthcare are provided by the eHealth Initiative (2008) and the Markle Foundation (2008). In the US, health information technology legislation (H.R. 6357) was introduced in 2008 to encourage adoption of a nationwide system of electronic medical records (US Congress 24 June 2008); this legislation, however, was not adopted into law. All of these advancements will undoubtedly lead to a reduction in unwarranted or mistaken prescribing and dispensing (as well as

improved patient compliance), with the obvious benefits accruing to human health and the economy as well as ecological impact. Of course, e-prescribing could also serve to increase the use of certain medications, as it is known, for example, that e-prescribing can increase compliance with filling prescriptions.

6.8 PharmEcovigilance: Vision for Optimal Integration of Medication's Environmental Footprint, Healthcare Effectiveness, and Sustainability

The concept of medications having "side effects" on the environment (e.g., Boxall 2002) poses the question of whether adverse effects in both humans and the environment should be treated as an integral whole. This idea has been formulated into a concept called ecopharmacology (Kümmerer and Velo 2006) and *pharmEcovigilance* (Daughton and Ruhoy 2008), which incorporate pharmacovigilance as applied to humans as well as to the environment. While post-marketing surveillance for adverse effects in humans is performed under traditional pharmacovigilance programs, these long-existing monitoring systems could be extended to also monitor for environmental impact – ranging from documenting sources of API release to the environment and API occurrence in various environmental compartments, to API impacts on non-target organisms. Currently, there is no formal program in place even for monitoring the occurrence and trends of APIs in the environment, or more importantly, for detecting the emergence in the environment of NMEs not previously used in commerce. An extraordinary opportunity could be gained to influence the evolving redesign of healthcare while improving its cost-effectiveness and quality by designing and implementing a pharmEcovigilance program. This would require collaboration among environmental scientists and healthcare professionals and others such as the medical insurance and pharmaceutical manufacturing industries.

The future of pharmaceuticals will be shaped by intrinsic forces ranging from: advances in technologies such as computational and synthetic chemistry (nanomaterials being one example) and bioinformatics; implementation of "green" approaches to the many facets of the lifecycle of APIs; advancement in the many fields of omics, especially metabolomics (Bernini et al. 2009); understanding of the human genome and epigenetics; the evolution and redesign in the way in which clinical medicine and pharmacy is administered and practiced; consumer expectations; and acceleration of translational research – shortening the time from basic to clinical research with faster adoption in clinical practice. Many of these forces are incorporated in the initiatives within the NIH's Roadmap for Medical Research (NIH 2008).

Extrinsic forces that will act as forcing functions could be dominated by climate change and the changing age structure of society. Climate change could dramatically influence the use of pharmaceuticals, as dictated by emerging or exacerbated problems surrounding cardiopulmonary and infectious diseases (e.g., vector

and water-borne), allergy, and physiological stresses (e.g., heatstroke), each having strong associations with the young and elderly (e.g., see: Ebi et al. 2006, Patz et al. 2005).

By analogy with the concepts of the "ecological footprint" (which quantifies the land area needed to sustain per capita living) (Rees 1992) and the derived concept of the "water footprint" – the water required to sustain a population (e.g., Hoekstra and Chapagain 2007) – perhaps the central question needing examination with respect to the sustainability of medication usage and the intersection between human and ecological health is "What types and quantities of medications are needed to optimize the health and well-being of society, while also protecting the integrity of the environment?" Can the prescribing and consumption of medication serve as an overall measure of societal and ecological health and well-being? A virtual healthcare system – one working perfectly – would generate no leftover medications.

A revolutionary strategy for inventory maintenance was developed by Henry Ford in the 1920s. Called Just-in-Time (JIT), it redefined any excess on-hand inventory as essentially being the equivalent of waste. Optimal performance required balance between demand and on-hand supply. If a concept analogous to JIT were applied to healthcare, medication waste could be viewed not only as a source of additional chemical contaminant burden for the environment, but also as a metric for inefficient, non-optimal health care (Daughton 2009). In a perfect, sustainable system, all humans and domestic animals would receive exactly the type, degree, and duration of treatment required for optimal and cost-effective therapeutic (and lifestyle or enhancement) outcomes, and any excreted residues of parent API or bioactive metabolites could be degraded in the environment with minimal adverse impact. Leftover drugs are diagnostic of any number of deficiencies in the chain of systems spanning from the design of drugs and packaging, advertising, prescribing, and dispensing, to ultimate patient use. Reducing the footprint of medication holds considerable potential for benefiting both human health and the environment.

US EPA Notice: The United States Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to the Agency's administrative review and approved for publication as an EPA document. Portions of this chapter were previously published in: Daughton CG and Ruhoy IS "Pharmaceuticals and Sustainability: Concerns and Opportunities Regarding Human Health and the Environment," In: A Healthy Future – Pharmaceuticals in a Sustainable Society, collaborative publication of Apoteket AB, MistraPharma, and Stockholm County Council, Sweden; Chapter 1, pp. 14–39, 2009.

References

Adam GIR, Sanders R, Jonsson J (1999) The development of pharmacogenomic models to predict drug response. Trends Biotechnol 17, 30–33

Anonymous (2008) List of withdrawn drugs. Wikipedia. http://en.wikipedia.org/wiki/List_of_withdrawn_drugs

Baird D (2003) Veterinary medicines in natural ecosystems: Assessing the risks. J Vet Pharmacol Therapeut 26, 28–29

Bajcar JM, Kennie N, Einarson TR (2005) Collaborative medication management in a team-based primary care practice: An explanatory conceptual framework. Res Social Adm Pharm 1, 408–429

BCG (December 2003) The hidden epidemic: Finding a cure for unfilled prescriptions and missed doses. The Boston Consulting Group. http://www.bcg.com/impact_expertise/publications/files/Hidden_Epidemic_Finding_Cure_Unfulfilled_Rx_Missed_Doses_Dec2003.pdf

Berenguer B, La Casa C, de la Matta MJ, Martin-Calero MJ (2004) Pharmaceutical care: Past, present and future. Curr Pharm Des 10, 3931–3946

Bernini P, Bertini I, Luchinat C, Nepi S, Saccenti E, Schäfer H, Schütz B, Spraul M, Tenori L (2009) Individual human phenotypes in metabolic space and time. J Proteome Res 8, 4264–4271

Borisy AA, Elliott PJ, Hurst NW, Lee MS, LehÃ¡r J, Price ER, Serbedzija G, Zimmermann GR, Foley MA, Stockwell BR, Keith CT (2003) Systematic discovery of multicomponent therapeutics. Proc Natl Acad Sci USA 100, 7977–7982

Boxall ABA (2002) The environmental side effects of medication – How are human and veterinary medicines in soils and water bodies affecting human and environmental health? Embo Reports 5, 1110–1116

Carbone AL, Song M, Uhrich KE (2008) Iodinated salicylate-based poly(anhydride-esters) as radiopaque biomaterials. Biomacromolecules 9, 1604–1612

Clark J, Summerton L, Smith E, Kampa E, Vidaurre R, Touraud E (2007) Discussion document on eco-pharmacostewardship. KNAPPE: Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters. http://www.knappe-eu.org/fichiers/47-D5.1%20Ecopharmacostewardship%20disc%20doc.pdf

Clayton TA, Baker D, Lindon JC, Everett JR, Nicholson JK (2009) Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. Proc Natl Acad Sci U S A (in press: 10.1021/pr900344m)

Connor S. Glaxo chief: Our drugs do not work on most patients. The Independent, Independent News and Media Limited, London, England, 8 December 2003 http://www.independent.co.uk/news/science/glaxo-chief-our-drugs-do-not-work-on-most-patients-575942.html

Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer JLJ, Linderman RJ, Lorenz K, Manley J, Pearlman Ba, Wells A, Zaks A, Zhang TY (2007) Key Green Chemistry research areas – a perspective from pharmaceutical manufacturers. Green Chem 9, 411–420

Costa LG, Eaton DL (eds.) (2005) Gene-Environment Interactions: Fundamentals of Ecogenetics. John Wiley & Sons, Hoboken, NJ

Crimmins WF (2001) Disposing of expired drugs: A matter of policy. J Am Vet Med Assoc 218, 10

Daemmrich A, Bowden ME (2005) Emergence of pharmaceutical science and industry: 1870–1930. Chem Eng News 83

Daughton CG (2002) Environmental stewardship and drugs as pollutants. The Lancet 360, 1035–1036

Daughton CG (2003) Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ Health Perspect 111, 757–774

Daughton CG (2004) PPCPs in the environment: Future research – beginning with the end always in mind. In: Kümmerer K (ed.) Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks, 2nd edn. Springer, Berlin, Germany

Daughton CG (2007) Pharmaceuticals in the environment: Sources and their management. In: Petrovic M, Barcelo D (eds.) Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle. Elsevier Science, Amsterdam

Daughton CG (2008) Pharmaceuticals as environmental pollutants: The ramifications for human exposure. In: Heggenhougen K, Quah S (eds.) International Encyclopedia of Public Health. Academic Press, Oxford, England

Daughton CG (2009) Chemicals from the practice of healthcare: Challenges and unknowns posed by residues in the environment. Environ Toxicol Chem 28, 2490–2494

Daughton CG, Brooks BW (2011 – tentative) Pharmaceutical active ingredients in aquatic organisms. In: Beyer WN, Meador J (eds.) Environmental Contaminants in Biota: Interpreting Tissue Concentrations, 2nd edn. Taylor and Francis, Boca Raton, FL

Daughton CG, Ruhoy IS (2008) The afterlife of drugs and the role of pharmecovigilance. Drug Safety 31, 1069–1082

Daughton CG, Ruhoy IS (2009) Environmental footprint of pharmaceuticals – the significance of factors beyond direct excretion to sewers. Environ Toxicol Chem 28, 2495–2521

DBU (2008) Strategies and perspectives for development, use and emission management of pharmaceuticals. 1st International Conference on Sustainable Pharmacy. Osnabrück, Germany, Deutsche Bundesstiftung Umwelt, 24–25 April. http://www.dbu.de/359.html

Ebi KL, Kovats RS, Menne B (2006) An approach for assessing human health vulnerability and public health interventions to adapt to climate change. Environ Health Perspect 114, 1930–1934

Eckerman I, Martineus J-C (1997) Medicines and the environment – what do we know today? In: Gray M (ed.) Swedish Association of Physicians for the Environment. Stockholm, Sweden. http://www.dnsy.se/_upload/lfm/medicines%20and%20the%20environment.pdf

eHealth Initiative (2008) eHealth Initiative. eHealth Initiative, Foundation for eHealth Initiative. Washington, DC. http://www.ehealthinitiative.org/

Ekedahl A (2002) Statistics on local drug sales: A tool to identify problem areas and to follow effects of education on drug use. Doctoral Dissertation, Department of Community Medicine, Malmö University Hospital, Lund University, Lund, Sweden, 54 pp, http://www.lub.lu.se/luft/diss/med638.pdf

Fichana D (2005) Green Engineering and Gate-to-gate Life Cycle Assessments for Pharmaceutical Products. Masters Dissertation, Rowan University, 142 pp, http://www.rowan.edu/library//rowan_theses/RU2005/0045GREE.PDF

Fugh-Berman A (2009). Speaking of Medicine: Medicine Community Blog, PLoS. http://speakingofmedicine.plos.org/2009/08/07/ghostwriting-101/

Galagan Y, Su WF (2008) Fadable ink for time-temperature control of food freshness: Novel new time-temperature indicator. Food Res Int 41, 653–657

Giacomini KM, Krauss RM, Roden DM, Eichelbaum M, Hayden MR, Nakamura Y (2007) When good drugs go bad. Nature 446, 975–977

Gorard DA (2006) Escalating polypharmacy. QJM 99, 797–800

Gunnarsson B, Wennmalm A (2008) Drug design should involve consideration of environmental risk and hazard. Lett Drug Des Discov 5, 232–235

HapMap (2008) International HapMap Project. The International HapMap Consortium. http://www.hapmap.org/

Haskell SRR, Ormond CJ, Occhipinti LP, Powers EL (2003) Waste management: Expired drugs. J Am Vet Med Assoc 223, 51–52

Henderson RK, Jimenez-Gonzalez C, Preston C, Constable DJC, Woodley JM (2008) EHS & LCA assessment for 7-ACA synthesis. A case study for comparing biocatalytic & chemical synthesis. Ind Biotechnol 4, 180–192

Hepler C, Strand L (1990) Opportunities and responsibilities in pharmaceutical care. Am J Health Syst Pharm 47, 533–543

HHS (2009) Nationwide Health Information Network (NHIN). U.S. Department of Health & Human Services. Washington, DC. http://healthit.hhs.gov/portal/server.pt?open=512&mode=2&cached=true&objID=1142

Hoekstra AY, Chapagain AK (2007) Water footprints of nations: Water use by people as a function of their consumption pattern. Water Resour Manage 21, 35–48

Hudson KL, Holohan MK, Collins FS (2008) Keeping pace with the times – the genetic information nondiscrimination act of 2008. N Engl J Med 358, 2661–2663

IMS (2008) IMS Health Forecasts 4.5 – 5.5 Percent Growth for Global Pharmaceutical Market in 2009, Exceeding $820 Billion. IMS Health Incorporated. http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=9e553599b554d110VgnVCM100000ed152ca2RCRD&vgnextfmt=default

IOM (2008) Knowing What Works in Health Care: A Roadmap for the Nation. Committee on Reviewing Evidence to Identify Highly Effective Clinical Services, Board on Health Care Services, Institute of Medicine, The National Academies Press, Eden J, Wheatley B, McNeil B, Sox H (ed). Washington, DC. http://www.nap.edu/catalog.php?record_id=12038

Joly BM, Polyak G, Davis MV, Brewster J, Tremain B, Raevsky C, Beitsch LM (2007) Linking accreditation and public health outcomes: A logic model approach. J Public Health Manag Pract 13, 349–356

Kaitin KI, (ed.) (2005) Drug safety withdrawals in the US not linked to speed of FDA approval. Tufts CSDD (Center for the Study of Drug Development) Impact Report 7, 1–4

Katsanis SH, Javitt G, Hudson K (2008) A case study of personalized medicine. Science 320, 53–54

Keil F (2008 – August) Pharmaceuticals for Human Use: Options of Action for Reducing the Contamination of Water Bodies: A Practical Guide. Institute for Social-Ecological Research (ISOE) GmbH and Research Project start ("Management Strategies for Pharmaceutical Residues in Drinking Water"). Frankfurt/Main, Germany. https://www.start-project.de/downloads/start_Practical_Guide.pdf

Khetan SK, Collins TJ (2007) Human pharmaceuticals in the aquatic environment: A challenge to green chemistry. Chem Rev 107, 2319–2364

Korobkin R, Rajkumar R (2008) The genetic information nondiscrimination act – a half-step toward risk sharing. N Engl J Med 359, 335–337

Krutzfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, Stoffel M (2005) Silencing of microRNAs in vivo with 'antagomirs'. Nature 438, 685–689

Kuehn BM (2008) Traces of drugs found in drinking water: Health effects unknown, safer disposal urged. J Am Med Assoc 299, 2011–2013

Kümmerer 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 Chem 9, 899–907

Kümmerer K, Velo G (2006) Ecopharmacology: A new topic of importance in pharmacovigilance. Drug Saf 29, 371–373

Kuspis DA, Krenzelok EP (1996) What happens to expired medications? A survey of community medication disposal. Vet Hum Toxicol 38, 48–49

Levy W (2008) Peptide progress: Refined manufacturing and delivery promises more advanced drug offerings. Pharm Formulation & Quality 10, 28–30, 32

Markle Foundation (2008) Connecting for Health. The Markle Foundation. http://www.connect-ingforhealth.org/

Martin-Calero MJ, Machuca M, Murillo MD, Cansino J, Gastelurrutia MA, Faus MJ (2004) Structural process and implementation programs of pharmaceutical care in different countries. Curr Pharm Des 10, 3969–3985

Mayer LD, Janoff AS (2007) Optimizing combination chemotherapy by controlling drug ratios. Mol Interv 7, 216–223

Microsoft (2009) Microsoft Amalga Unified Intelligence System 2009. Microsoft. http://www.microsoft.com/amalga/products/microsoftamalgauis/default.mspx

Mihelcic JR, Zimmerman JB, Ramaswami A (2007) Integrating developed and developing world knowledge into global discussions and strategies for sustainability. 1. Science and Technology. Environ Sci Technol 41, 3415–3421

Moynihan R (2008) Key opinion leaders: Independent experts or drug representatives in disguise? British Medical Journal 336, 1402–1403
NIH (2008) NIH Roadmap Initiatives. Office of Portfolio Analysis and Strategic Initiatives, National Institutes of Health Bethesda, Maryland. http://nihroadmap.nih.gov/initiativeslist.asp
Patz JA, Campbell-Lendrum D, Holloway T, Foley JA (2005) Impact of regional climate change on human health. Nature 438, 310–317
Pearson GJ (2007) Evolution in the practice of pharmacy–not a revolution! CMAJ 176, 1295–1296
Phillips DP, Barker GEC, Eguchi MM (2008) A steep increase in domestic fatal medication errors with use of alcohol and/or street drugs. Arch Intern Med 168, 1561–1566
Pinheiro C (2008) Drug donations: What lies beneath. Bull World Health Organ 86, 580–581
Pollack A. Pricing Pills by the Results. New York Times, New York Times, 14 July 2007 http://www. nytimes.com/2007/07/14/business/14drugprice.html?ref=health&pagewanted=all
PricewaterhouseCoopers (2005) Personalized medicine: The emerging pharmacogenomics revolution. PricewaterhouseCoopers GTC, Health Research Institute. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf
Rahman SZ, Khan RA (2006) Environmental pharmacology: A new discipline. Indian J Pharmacol 38, 229–230
Rees WE (1992) Ecological footprints and appropriated carrying capacity: What urban economics leaves out. Environ Urban 4, 121–130
Rosenberg J, Schilit S, Nathan J (2008) Which oral solid medications should be protected from light and/or moisture? Drug Topics 12 May, 25–27
Ruhoy IS, Daughton CG (2008) Beyond the medicine cabinet: An analysis of where and why medications accumulate. Environ Int 34, 1157–1169
SACGHS (May 2008) Realizing the Potential of Pharmacogenomics: Opportunities and Challenges. Secretary's Advisory Committee on Genetics, Health, and Society, chartered by U.S. Department of Health & Human Services (ed). http://www4.od.nih.gov/oba/sacghs/reports/SACGHS_PGx_Report.pdf
Sanderson K (2009) Big interest in heavy drugs. Nature 458, 269
Siddiqui IA, Adhami VM, Bharali DJ, Hafeez BB, Asim M, Khwaja SI, Ahmad N, Cui H, Mousa SA, Mukhtar H (2009) Introducing nanochemoprevention as a novel approach for cancer control: Proof of principle with green tea polyphenol Epigallocatechin-3-Gallate. Cancer Res 69, 1712–1716
Sismondo S (2007) Ghost management: How much of the medical literature is shaped behind the scenes by the pharmaceutical industry? PLoS Med 4, e286
Smolensky MH, Peppas NA (2007) Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Deliv Rev 59, 828–851
Stockholm City Council (2008) Environmentally Classified Pharmaceuticals. http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=10205; via www.janusinfo.se/environment
Stoughton M, Votta T (2003) Implementing service-based chemical procurement: Lessons and results. J Cleaner Production 11, 839–849
Surescripts (2009) 2008 National Progress Report on E-Prescribing. Alexandria, VA: Surescripts LLC. http://www.surescripts.com/downloads/NPR/national-progress-report.pdf
Thayer AM (2008) Filling a highly potent niche: Drug companies want to create conjugates of potent drugs and biological molecules, and custom manufacturers are complying. Chem Eng News 86, 28–32
Tinetti ME (2008) Over-the-counter sales of statins and other drugs for asymptomatic conditions. N Engl J Med 358, 2728–2732
Trusheim MR, Berndt ER, Douglas FL (2007) Stratified medicine: Strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov 6, 287–293
Tucker JL (2006) Green chemistry, a pharmaceutical perspective. Org Process Res Dev 10, 315–319
Tudor TL (2007) Towards the development of a standardised measurement unit for healthcare waste generation. Resour, Conserv Recycling 50, 319–333

UNIDO (2008) Chemical Leasing. United Nations Industrial Development Organization. Vienna, Austria. http://www.chemicalleasing.com/

US Congress (24 June 2008) H.R. 6357: PRO(TECH)T Act of 2008 ("Protecting Records, Optimizing Treatment and Easing Communication through Healthcare Technology Act of 2008") 110th Congress, 2D Session, Washington, DC

US EPA (2008a) Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature. US Environmental Protection Agency. http://www.epa.gov/ppcp/lit.html

US EPA (2008b) Green Chemistry Program at EPA. U.S. Environmental Protection Agency. http://www.epa.gov/gcc/pubs/epa_gc.html

US FDA (2008a) Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Rockville, MD. http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

US FDA (2008b) FDA's Sentinel Initiative: National Strategy for Monitoring Medical Product Safety. US Food and Drug Administration. http://www.fda.gov/oc/initiatives/advance/sentinel/

van Mil JWF, Schulz M, Tromp TFJD (2004) Pharmaceutical care, European developments in concepts, implementation, teaching, and research: A review. Pharm World & Sci 26, 303–311

Venhuis BJ, Barends DM, Zwaagstra ME, de Kaste D (2007) Recent developments in counterfeits and imitations of Viagra, Cialis and Levitra: A 2005–2006 update. RIVM Report 370030001/2007. Bilthoven, the Netherlands: RIVM (Netherlands National Institute for Public Health and the Environment). http://rivm.openrepository.com/rivm/handle/10029/16459?mode=full

Warner S (2004) Diagnostics + therapy = theranostics. The Scientist 18, 38

White EV, Latif DA (2006) Office-based pharmacy practice: Past, present, and future. Ann Pharmacother 40, 1409–1414

WHO (1999) Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies. World Health Organization. http://www.who.int/water_sanitation_health/medicalwaste/pharmaceuticals/en/index.html

WHO (2007) WHO core principles for achieving safe and sustainable management of healthcare waste. World Health Organization, Department for Public Health and Environment, Assessing and Managing Environmental Risks to Health, WHO/SDE/WSH/07.10. http://www.who.int/water_sanitation_health/medicalwaste/hcwprinciples.pdf; http://www.who.int/water_sanitation_health/medicalwaste/hcwprinciples/en/index.html

WHO (2008a) "World directory of poisons centres (Yellow Tox)" International Programme on Chemical Safety (IPCS). The World Health Organization. Geneva, Switzerland. www.who.int/ipcs/poisons/centre/directory/en/

WHO (2008b) About the ATC/DDD system. The WHO Collaborating Centre for Drug Statistics Methodology. Oslo, Norway. http://www.whocc.no/atcddd/atcsystem.html

Woodend K (2003) Medication management: The future of pharmaceutical care? Can Pharm J (CPJ) 136, 29–31, 46

Woodley JM (2008) New opportunities for biocatalysis: Making pharmaceutical processes greener. Trends Biotechnol 26, 321–327

Woodward KN (2005) Veterinary pharmacovigilance. Part 3. Adverse effects of veterinary medicinal products in animals and on the environment. J Vet Pharmacol Therapeut 28, 171–184

Zed PJ, Abu-Laban RB, Balen RM, Loewen PS, Hohl CM, Brubacher JR Wilbur K, Wiens MO, Samoy LJ, Lacaria K, Purssell RA (2008) Incidence, severity and preventability of medication-related visits to the emergency department: A prospective study. CMAJ 178, 1563–1569

Zuccato E, Calamari D, Natangelo M, Fanelli R (2000) Presence of therapeutic drugs in the environment. The Lancet 355, 1789–1790

Part II
Development, Synthesis and Production and Distribution of Pharmaceuticals

Chapter 7
Ecopharmacostewardship – A Pharmaceutical Industry Perspective

David Taylor

Until the late 1990s, the environmental impact of the pharmaceutical industry was universally considered to be very minor. Any environmental impact was considered to arise from manufacturing facilities and these were relatively small in size with well controlled emissions. It was appreciated that the pharmaceuticals themselves were biologically active, but in view of the small quantities being manufactured and the high cost of production, releases to the environment from manufacturing were expected to be very small.

However the discovery of pharmaceutical residues in surface waters from 1994 onwards led to this view being revised. Although the presence of pharmaceutical residues in surface waters had been predicted by Richardson and Bowron (1985) in the mid 1980s, it was not for another decade until such residues began to be routinely measured following the identification of clofibric acid in German rivers by Stan et al. (1994). Residues have now been found in groundwaters, estuarine and coastal waters and some compounds have been detected in drinking water. Concentrations of pharmaceuticals in surface waters now appear to be ubiquitous although they are rarely found above 0.1 μg/l and are frequently below 0.01 μg/l (Alder et al. 2006). Concentrations in wastewaters are usually in the μg/l range but in some cases much higher values have also been reported (see later)

We now know that pharmaceuticals can enter the environment in three different ways: in effluents discharged from manufacturing sites, from the disposal of unused and life expired medicines, and via excretion from the patient. Detailed quantification for any individual pharmaceutical is difficult, but there is general agreement that the latter source dominates the global environmental input, with effluent discharges and the disposal of unused medicines making a relatively small contribution (Halling-Sørensen et al. 1998, Kümmerer 2004). Relatively high local concentrations can occur adjacent to discharges from industry, particularly in developing countries (Larsson et al. 2007) and hospitals (Thomas et al. 2007).

D. Taylor (✉)
WCA Environment Limited, Oxfordshire SN7 7YR, UK
e-mail: david.taylor@wca-environment.com

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_7,

Most scientists, in academia, governments, regulatory bodies and industry that have evaluated the published data have concluded there appear to be no appreciable acute aquatic life effects due to pharmaceuticals in the environment (Cunningham et al. 2006). In other words short term immediate damage to the environment is very unlikely. However, work continues on evaluating potential chronic effects in order to refine these assessments. One area of focused effort concerns certain hormones because they are potentially a class of compounds with observable effects at environmentally relevant concentrations. However, as research accumulates it is becoming clear that hormonally active compounds do not all have similar properties and thus such medicines need to be considered on a case by case basis rather than as a single class. Scientific knowledge of the potential long-term effects of pharmaceuticals in the environment on plants and wildlife is still in the early stages of development and is an active area of research.

Consequently it has now been recognised that product stewardship is just as relevant to human medicines as to other products and the term ecopharmacostewardship is now being used to describe the environmental aspects of pharmaceutical product stewardship. Product stewardship is a principle that directs all participants involved in the life cycle of a product to take shared responsibility for the impacts on human health and the natural environment that result from the production, use, and end-of-life management of the product. The greater the ability of a party to influence the life cycle impacts of a product, the greater the degree of that party's responsibility. The stakeholders typically include manufacturers, retailers, consumers, and government officials (Anon 2007b).

7.1 The Stakeholders

In the pharmaceutical industry we can identify five key stakeholders: the innovator, the manufacturer, the regulator, the health professional and the patient, all of whom have responsibilities to protect the environment from unnecessary damage.

The pharmaceutical industry is a highly unusual one for two reasons. Firstly, the costs of new product development are extremely high when compared to the cost of manufacture. Secondly, new innovations tend to add to the overall availability of medicines rather than replacing existing products. As a consequence the industry has developed in two separate ways. A high risk/high profit innovation sector and a low risk/low profit generic manufacturing sector. Thus, the vast majority of new pharmaceuticals are developed by a small number of well known research pharmaceutical companies such as AstraZeneca, Bristol-Myers Squibb, GSK, Johnson & Johnson, Lilly, Merck, Pfizer, Roche, Sanofi-Aventis and Wyeth whereas the bulk of existing medicinal products is supplied by a wide range of generic manufacturers, whose names are largely unknown to the public. This means that, at any point in time, the innovating research pharmaceutical companies are selling only ca. 10–20% (by volume) of the medicines being taken by patients, the remainder being produced by generic companies.

Product innovation is a very high risk business. It costs a very large amount of money, $500–$800 m, to take a new compound from the laboratory bench to the

patient and the success rate is extremely low, with only one or two out of every 100 compounds entering clinical development resulting in a marketable product. This means that a large proportion of the research into new medicines does not lead to any subsequent income. The innovating company does have exclusive rights to sell a new product until the patent protection expires in order to recover its costs and generate profits to fund further investment. However the development process is lengthy and it can take 10–12 years between granting the patent to launching the product, which leaves only 8–10 years of exclusive sales. Although a successful pharmaceutical will eventually become well known to all doctors, this will take several years. Consequently research pharmaceutical companies must also engage in a large amount of marketing to ensure that the value of the new drug becomes widely known as fast as possible. This cost is additional to the $500–$800 m already spent in drug development.

When the patent protection of a successful new pharmaceutical expires, its manufacture and sale is usually rapidly taken over by one of the many "generic" pharmaceutical companies. This is a very low risk activity. In general these companies are not involved in new product development and, since at the end of its patent life the drug is already a successful and well known product, there is much less need for sales and marketing. Manufacturing costs are also relatively small and thus, post patent expiry, the price of a new pharmaceutical falls dramatically.

The pharmaceutical industry is, not surprisingly, very highly regulated. The research, clinical trials and manufacturing are covered by rigorous compliance regulations with the objective of ensuring consistent high quality. These Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) regulations are strictly enforced and subject to random inspection. In addition, no new medicinal product can be introduced onto the market until the appropriate medicines regulator, such as the European Medicines Evaluation Agency (EMEA) or the Federal Drug Administration (FDA) has approved its safety, effectiveness and quality. The approval process is dominated by considerations of human safety but also includes an assessment of environmental risk. Although, at least in the European Union, the environmental risk will not be used to prevent the approval of a marketing authorisation, such information may be used by environmental regulators to control the subsequent emissions of the pharmaceutical in wastewaters. This is very different to the position of veterinary pharmaceuticals where the environmental risk assessment data can be used directly to prevent approval.

Health professionals determine which pharmaceutical is prescribed. Their key responsibility is to do what is best for the patient but their method of prescribing can influence the amount of unused or life expired medicines. Finally the patient has a role to play in appropriately managing the disposal of unwanted medicines (see Castensson and Ekedahl, Chap. 12, and Vollmer, Chap. 11, this book).

The Research Pharmaceutical Industry is clearly one of the major stakeholders in ecopharmacostewardship and the remainder of this chapter describes the way in which these companies are fulfilling that responsibility

7.2 Greener Drug Design

In recent years there have been many suggestions that, in the light of the discovery of residues of pharmaceuticals in water, the pharmaceutical industry should begin to produce "green" drugs (Daughton 2003, Kümmerer 2007, Kümmerer, Chaps. 1 and 9, this book). This then raises the question of how green is the present generation of drugs. The most comprehensive data that currently exist come from the Swedish Environmental Classification system (Mattson et al. 2007). This categorises drugs into five classes based on their risk to the environment. Table 7.1 shows the current output.

It can clearly be seen from this table that 97% of the 300 pharmaceuticals so far assessed pose an insignificant or low risk to the environment with only two out of 300 that fall into the high risk category. A recent study, part of the KNAPPE[1] project carried out under the European Union Framework 6 programme, has produced a similar outcome (Boxall et al. 2008). They report that "a large body of literature is now available on the ecotoxicity of pharmaceuticals *and that analysis of this standard data (and monitoring data) indicates that risks of most substances (and mixtures) are low.*" Consequently this section is entitled "greener" drug design.

If the known environmental risks appear to be very low, why is there a need to produce even "greener" pharmaceuticals? The rationale for this is based on the Precautionary Principle. Since these molecules are designed to have biological effects it would be prudent if residues in the environment could be reduced to the lowest possible level. This may indeed be desirable but actions taken to achieve this must not impact negatively on patient care and should not inadvertently produce other negative impacts on the environment. For example increasing water or wastewater treatment will require additional energy which may in turn increase emissions of greenhouse gases.

Table 7.1 Summary of LIF database

Risk ratio (PEC/PNEC)	No.	% (excluding "exempt" and "insufficient data")	% (excluding "insufficient data")
Exempt substances	150		93
Insignificant risk (<0.1)	127	85	
Low risk (0.1–1.0)	12	8	4
Medium risk (1.1–10)	9	6	3
High risk (>10)	2	<2	<1
Insufficient data to classify	150		
Total	450		

"Exempt" substances are those identified by the European Medicines Evaluation Agency (EMEA) as not requiring an environmental risk assessment "because they are unlikely to result in significant risk to the environment" (Anon 2007a).

[1] Knowledge and need assessment of pharmaceutical products in environmental waters [www.knappe-eu.org].

7.2.1 Degradable Pharmaceuticals

The objective of "greener" drug design is to produce drugs which leave lower residues in the environment (see Kümmerer, Chaps. 1 and 9, this book). A number of environmental scientists have made the assumption that this means that all new drugs should be biodegradable. Indeed there are a number of drugs that are biodegradable, although they were not designed to be so. However this somewhat simplistic approach, even if it were possible to realise, would not be a panacea and is certainly not simple to accomplish given our current state of knowledge.

Medicines, like most products, do not need to be 100% persistent throughout their life-cycle. However they do need to be functionally persistent. In other words the medicine has to be stable enough to remain unchanged during a realistic shelf life and to be able to be transported, unchanged, though various pathways in the body to reach the site where its effect will be exerted. Since most medicines are taken orally, this means being able to transit through the highly acidic stomach. Not only is stability needed for the medicine to be effective, instability can result in side effects caused by the toxicity of breakdown products, particularly in the liver. The ideal drug would therefore be a substance which only began to break down after it had been excreted by the patient.

With the current state of scientific knowledge it is probably not yet possible to design such a drug ab initio. We do not yet have sufficient understanding of chemistry, pharmacology, toxicology and toxicokinetics to be able to design new medicines by using molecular engineering to produce the perfect molecule. The reality is that most drugs are simple modifications of substances that are "discovered" to have the appropriate biological activity as a result of the simple screening of very large "chemical libraries" which contain several million substances. The screening process may identify a number of interesting leads which can then be subjected to further investigation to establish both their efficacy and safety. The most interesting two or three molecules will then be subjected to further chemical and physical manipulation to try to maximise the efficacy whilst minimising any safety issues. This is a very challenging process since efficacy and safety are often inversely related. Promising molecules then proceed for further development; however the success rate from this point onwards is still very poor with less than 1 in 100 candidates making it to eventual marketing authorisation. Our understanding of how molecules degrade in the environment is simply insufficient at present to optimise for environmental degradability as well. This does not mean that changes during lead optimisation will have no effect on degradability; sometimes the optimised lead is indeed more degradable in the environment (Kümmerer et al. 2000). However, this currently occurs by chance rather than by any structured design.

Despite these challenges, far-sighted pharmaceutical companies are considering what could be done to improve knowledge in this area. A study, commissioned jointly by AstraZeneca and the Royal Society of Chemistry (Clarke and Summerton 2010) reviewed current knowledge and experience of ab initio "green" drug design. They concluded that little was known. Although there is some empirical knowledge which has been used to produce computerised predictive models, one of the key

problems was the lack of fundamental understanding of the relationship between molecular structure and degradation in the environment. In the absence of this information it is impossible to predict with any degree of certainty what impact changes in the molecular structure of a candidate drug might have on its ultimate environmental degradability. Rapid advances in this area therefore seem to be unlikely. However, it might be possible to generate some simple guidelines, derived from empirical data on existing pharmaceuticals that might aid drug development. Much of the available information on the persistence of pharmaceuticals should soon be available in the LIF Environmental Classification Database (Mattson et al. 2007).

However, producing drugs that are more degradable in the environment will not necessarily eliminate environmental residues. The very low environmental residues that are currently being detected represent the equilibrium concentration reached between a constant input from wastewater treatment plants and the degradation rate in the environment. The data from the Swedish Environmental Classification Scheme (Mattson et al. 2007) demonstrates that although few existing medicines are rapidly degraded in the environment, relatively few of them are highly persistent and most pharmaceuticals appear to degrade, albeit slowly. Increasing the degradation rate of new pharmaceuticals would undoubtedly reduce the current residue levels found in the environment but, even with existing analytical methodology, it is highly likely that residues at lower levels would still be detectable.

7.2.2 Current Improvements in Drug Design

The design of greener drugs needs to be much more holistic and address the wider question of how can we produce drugs that leave lower environmental residues. Clearly increased degradability is one method, but there are others which, at least in the short term, are likely to prove more successful.

The fundamental driver of drug discovery research is to identify the perfect human medicine. Table 7.2 shows several of the pharmacological objectives that would deliver improved patient benefit, alongside the environmental improvements that would ensue if that objective was reached.

The first three of these would lead to lower residues of active substances entering the environment, in other words reduction at source. The last two would lead to even lower potential impact of the residual active material on ecosystems.

Table 7.2 Comparison of human and environmental requirements for new drugs

Drug design criteria	Environmental significance
100% oral absorption	Lower emissions from patients
Metabolised in patient to inert substances	Releases only inert residues
Effective in all patients treated	Produces lower overall drug use
Disease receptor specific	No impact on healthy receptors
No effects other than therapeutic ones	No non target effects

Current developments are already leading to candidate drugs with a lower potential for environmental impact. For example a better understanding of drug metabolism and pharmacokinetics can result in lower doses being administered to achieve the same therapeutic effect. Similarly, shorter duration of therapy, better targeting and improved drug delivery combined with increased specificity all lead directly to smaller emissions from the patient to the environment and thus lower environmental residues.

For example, AstraZeneca is currently pursuing a major programme of research into tuberculosis (TB) at its Indian research and development facility in Bangalore (IFPMA 2008). The project is dedicated to finding a new therapy for TB that will act in drug-resistant disease and reduce the complexity or the duration of treatment. Current therapy for tuberculosis is 40 years old and requires a combination of five drugs to be taken over a minimum period of six to 8 months. The desired endpoint of the research is a single drug therapy that will be effective in 4 months. Shortening the duration of therapy will improve patient compliance leading to lower numbers of relapses. This together with replacing five drugs with a single therapy would lead to a very significant reduction in the amounts of drugs entering the environment.

In addition to this steady incremental improvement, two revolutionary aspects of pharmaceutical development will mean that the next generation of pharmaceuticals will produce much lower environmental residues than the current formularies.

The first of these is the advance of biopharmaceuticals (see Straub, Chap. 8, this book). The vast majority of current pharmaceuticals consist of relatively small molecules produced by chemical synthesis. However, advances in our understanding of genomics and proteomics coupled with our increasing technological capability to manufacture very large molecules is leading to a very rapidly growing interest in the use of biological as opposed to chemical based therapies. The first biopharmaceutical was approved in 1980 and by 2004 there were 108 biological pharmaceuticals that had been approved for sale by the US FDA and a further 324 were under development. In 2009 it is expected that biopharmaceuticals will account for 15% of the total sales value of pharmaceuticals and it is estimated that this area now accounts for more than 30% of all drugs in development.

The fastest growth is in the area of monoclonal antibodies which are components of the human immune system and are considered by some to be the perfect human medicines. They have major therapeutic advantages. Their high potency means that patient doses can be small which subsequently then requires only small scale manufacture. They have exquisite specificity and can be targeted to human receptor subtypes responsible for pathology or disease, thus they have substantially less potential for side effects. These proteins are then rapidly metabolised by the human body to produce fragments with no mammalian biological activity, thus avoiding the possibility of producing metabolites with undesirable pharmacological activity.

From an environmental perspective biopharmaceuticals appear to offer major advantages; most of these compounds produce little if any residues of the active substance, which is in any case much less likely to exert any adverse impact on the ecosystem, since it is specifically designed to interact only with a diseased human receptor. However, the full environmental relevance of these substances is not yet

clear. Biopharmaceuticals are not all easily biodegraded, and modified natural compounds even less so. Structurally related compounds such as plasmids have already been detected in the environment and it is known that the protein structures known as prions[2] are very environmentally stable.

The second therapeutic revolution also stems from our improved understanding of genomics, although it is still in its infancy. This is the area of "personalised medicine". It has been known for many years that most pharmaceuticals do not work successfully in all patients. It was suspected that this was due to the slightly different genetic makeup of individual patients, but lack of appropriate experimental techniques meant that this could not be further investigated. However, the recent rapid advances in the mapping of the human genome and subsequent development of the scientific disciplines of genomics, proteomics and metabolomics is leading us to a better understanding of the molecular signals of many diseases. The expectation is that molecular screens combined with clinical data will point to more precise treatment options for each patient sub-group. This will enable much more precise and effective prescribing to occur which will, in turn, mean less overall drug use since every prescribed dose will be effective first time.

Thus we can see that if it proves impossible to design degradability into all new pharmaceuticals, nevertheless current and future successes in drug development will mean that future generations of pharmaceuticals will result in lower environmental residues. In some cases, as now, where the drug is completely metabolised by the patient, there will be no residual active material in the environment. However, in most cases residues will still be present and, with further advances in analytical science, are likely to remain detectable.

7.3 Sustainability in Research, Manufacturing, Sales and Distribution

The core of ecopharmacostewardship relates to the pharmaceutical product itself. However, these products need to be invented, manufactured, distributed and sold and, like all other business activity, these processes also have an impact on the environment.

Stewardship activities in the research pharmaceutical sector are focussed on minimising its environmental footprint and reducing the subsequent pressure of the residual footprint on the environment (for a broader view see Läufer, Chap. 5, this book). Consequently the industry is implementing sustainable consumption and production techniques to minimise the total resources consumed per patient treated. It is also managing any residual risks to minimise potential environmental impacts from its business activities. These activities fall into two areas; the application of "green

[2] Prions cause a number of diseases in a variety of animals and Creutzfeldt-Jakob disease (CJD) in humans.

chemistry and technology" techniques in R&D and process design and secondly the application of "lean engineering" to facility construction and management.

7.3.1 Sustainability in R&D and Manufacturing

The twelve principles of Green Chemistry were first formulated by Anastas and Warner (1998). Since then they have been actively taken up by the pharmaceutical sector in the process design area and are now reaching further upstream, influencing medicinal chemists in research and development laboratories. Unlike the majority of "bulk" chemicals, most pharmaceuticals are very complex organic molecules that have to be constructed using multiple synthetic steps, often involving the isolation and purification of intermediate products. As a consequence process efficiency has historically been very low (Sheldon 1994). In recent years, driven by both cost and sustainability issues, the research pharmaceutical companies have become industry leaders in the introduction of green chemistry and technology techniques into their process design. Companies have developed expert systems to ensure that potential environmental consequences, as well as health and safety considerations, are taken into account in the selection of reagents and solvents (Curzons et al. 1999) and sustainability metrics are now routinely used to compare alternative process routes. This has led to major improvements in efficiency in these complex syntheses (Dunn et al. 2010) and pharmaceutical companies regularly win US Presidential Green Challenge Awards (EPA 2008). The major companies are also now collaborating at the American Chemical Society Green Chemistry Roundtable and sponsoring research that should lead to even more sustainable synthesis routes (Crow 2008).

Solvents comprise the largest part of the waste produced in pharmaceutical manufacture and extensive recycling and reuse of solvents is undertaken to minimise resource consumption. Solvents that cannot be reused or further recycled are incinerated, usually in installations which can recover the energy.

As discussed previously, the pharmaceutical industry is now beginning to explore the new area of biopharmaceuticals. Few of these have yet reached the patient and their manufacture at full scale will provide new sustainability challenges. The active ingredients, often protein based, are too large and complex to be synthesised by conventional chemical techniques. As a result current biopharmaceuticals tend to be manufactured in cell cultures using fermentation methods which can produce very large volumes of very low strength effluents. A more resource efficient method of producing the small amounts of material needed might be by stimulating the formation of the appropriate substance in an animal or plant, a practice known as "pharming". For example an anti thrombin, known as ATRyn licensed by EMEA (2007) is extracted from the milk of goats that have had a gene (DNA) inserted which makes them able to produce the human protein in their milk. A substantial body of research is also now available on the use of genetically engineered plants, particularly cereals to produce pharmaceuticals (Ramessar et al. 2008). The use of genetically engineered plants and organisms in this way has major advantages

since the biopharmaceutical molecule would be very difficult or impossible to produce using conventional chemical synthesis. However, it raises a number of ethical issues, particularly when higher organisms are used in this way and a considerable debate can be expected to take place over the next few years. In addition, the use of genetically engineered plants remains a controversial area in terms of their potential environmental impact.

Once the active ingredient has been produced it must then be formulated into the final medicine, e.g. turned into a tablet, a cream or an inhaler before being packed and distributed. Since this increases both the weight of the finished product and its packaging, secondary manufacture is frequently undertaken close to the point of sale. This improves the ability to react quickly to changes in demand whilst also reducing the need to transport material over long distances. This brings benefits in terms of security as well as reducing transport related emissions. Although the formulation aspects of manufacture do not involve chemical synthesis, they can generate significant waste streams, mainly associated with cleaning of equipment to avoid cross contamination. Historically, cleaning procedures used significant quantities of organic solvents which then had to be disposed of using incineration. In recent years aqueous cleaning systems have been introduced. Although this produces much larger volumes of waste, these very dilute solutions are readily treatable using modern technologies such as reverse osmosis and activated carbon with potential for reuse of the recovered water.

Manufacturing plants can be a source of pharmaceuticals entering the environment, although this is considered to be very small compared to that resulting from patient use. Larsson et al. (2007) demonstrated that a small number of effluent samples entering the environment, taken from a common treatment facility serving a group of generic pharmaceutical manufacturing plants in India, contained active pharmaceutical ingredients at concentrations up to 30 mg/l. However, data produced by AstraZeneca (see case study below) for internal monitoring purposes shows that this may not be representative of factories which manage their waste water effectively, e.g. with custom built treatment facilities. In such cases concentrations of active ingredients in effluent discharges can be controlled to <0.01 mg/l.

Case Study: AstraZeneca has two major manufacturing and research sites in the town of Södertälje, Sweden. These employ ca. 7,200 people and the combined wastewater of both sites is treated in a plant at Gärtuna specifically designed to treat waste from pharmaceutical manufacture. The effluent is collected in 4,000 m^3 balancing tanks, before being fed to a multistage physical, biological and chemical treatment plan, which involves pH control, fungal and bacterial reactors, carbon adsorption, chemical precipitation and sand filtration stages. The treated wastewater is discharged into Hallsfjärden. The data in the following table represent the concentrations of 10 active pharmaceutical ingredients that were measured in three 24 h composite samples of the final discharge to the environment, collected over a 12 week period, from the site effluent treatment plant.

Finally, the medicine needs to be protected for its journey from the formulation plant via the distribution chain and the pharmacy to the individual patient. Minimising packaging has also been the focus of much effort in the industry,

Substance	Effluent concentration (μg/l)			PEC (μg/l)	PNEC (μg/l)	PEC/PNEC
	Sample 1	Sample 2	Sample 3			
Bambuterol	6.8	6.4	3.1	0.0068	71	<0.01
Budesonide	<0.10	<0.050	<0.050	<0.0001	8.6	<0.01
Bupivacaine	0.12	2.3	0.12	0.0023	39	<0.01
Candesartan cilexetil	<0.10	<0.10	<0.25	<0.00025	0.012	<0.02
Felodipine	0.040	0.31	0.046	0.00031	0.05	<0.01
Lidocaine	0.20	0.84	0.082	0.00084	106	<0.01
Mepivacaine	0.46	4.9	0.24	0.0049	59	<0.01
Metoprolol	1.95	2.2	0.77	0.0022	58.3	<0.01
Ropivacaine	8.4	31	4.3	0.031	34	<0.01
Terbutalin	<0.010	<0.025	<0.050	<0.00005	240	<0.01

Notes: The predicted environmental concentrations (PEC) were calculated from the maximum concentration in the 3 samples divided by the measured dilution factor of 1,000× available in the receiving water 200 m from the discharge point. The predicted no-effect concentrations (PNEC) are derived from internal experimental data, mainly *Daphnia sp* 28d EC_{50} values.

although these have sometimes been impeded by other, often desirable, legislative requirements; e.g. loose tablets now have to be encapsulated in blister packs as a child protection measure and pharmaceutical labels must now include information in Braille to improve accessibility (EC 2004). Both of these laudable pieces of regulation have resulted in increased amounts of packaging.

So far we have only considered the sustainability challenges caused by the product. However in terms of stewardship we also need to consider the environmental impact of the facilities in which these activities take place. The key impacts relate to energy and water consumption with a secondary issue of potential biodiversity impact.

It might seem obvious that the factories producing the bulk active ingredients would dominate the overall energy signature. In fact more energy is consumed by AstraZeneca's research laboratories, mainly in operating fume cupboards, than by its factories, so a holistic approach needs to be taken to minimising energy use. These issues are being addressed in the industry within global programmes to reduce energy consumption and simultaneously to reduce the carbon intensity of the energy sources used. Most research pharmaceutical companies have set themselves targets to reduce their energy demand dramatically as well as cutting their emissions of greenhouse gases. For example GlaxoSmithKline has a target to reduce its energy use in operations and transport by 20% in the 5 years to 2010 (GlaxoSmithKline 2007). In a similar way many pharmaceutical companies are pursuing aggressive policies to reduce their consumption of water, particularly in those regions of the world where water supplies are under stress. For example Pfizer reduced its consumption of water by 33% between 2003 and 2006 (Pfizer 2007). The pharmaceutical industry has relatively little direct impact on biodiversity. However, like all

businesses its operational facilities can impact on the local biodiversity. Most pharmaceutical companies have implemented biodiversity action plans in line with the 1992 UN Convention on the Conservation of Biodiversity (United Nations 2002) and some have adopted major public commitments, e.g. Bristol-Myers Squibb committed themselves "to protect land equal in area to the amount of land used by our research and development, manufacturing, distribution centres, and administrative offices by 2010" a target that they exceeded in 2007 (BMS 2007).

Finally, there are two other areas where the industry might have an impact on biodiversity, these very different areas relate to bioprospecting and the use of genetically engineered organisms in manufacturing. Many of the drugs in use today had their origin in natural constituents of plants and some companies still have an interest in sourcing new compounds for their compound libraries from the natural environment. These searches are now carried out in line with the UN Biodiversity Convention, which ensures that the environment is protected and that indigenous communities share in any benefits that result. As discussed above the growing interest in biopharmaceuticals is leading to an increase in the use of genetically engineered organisms to manufacture these very large and complex molecules. The scale of these operations is small since, in view of the potency of their effects, only small amounts of material need to be manufactured. However, strict controls are necessary to ensure that human and animal food chains are not contaminated and that any potential impact on biodiversity is minimised. This is an area of considerable public and scientific discussion where more research work is needed.

7.3.2 Sales and Distribution

At first sight Sales and Distribution may appear to have little relevance to sustainability, but there are also significant challenges in this area. Research companies need to ensure that any new medicine is brought rapidly to the attention of as many doctors as possible. This has traditionally been done by using sales representatives who call personally on doctors to provide them with information. A major company will usually have a large sales force whose only efficient means of transport will be the motor car. In 2007 AstraZeneca reported that business travel by car, 90% of which was associated with sales and marketing, amounted to 730 million km, a distance equivalent to 18,300 times around the world which produced 150,000 tonnes of greenhouse gas emissions (AstraZeneca 2008). Companies are tackling this in two ways: the immediate objective is to improve the efficiency of road travel by using more efficient vehicles and extending driver training to include eco-driving techniques. In the longer term e-commerce techniques may dramatically reduce the need for direct contact between the sales force and the individual doctor.

AstraZeneca has been increasing the efficiency of its vehicle fleet for many years by using smaller and more efficient vehicles. It is now extending this programme by introducing both "hybrid vehicles" and "flex fuel" vehicles into its sales fleet In Brazil where sustainably derived ethanol fuels are widely available, more than

96% of the cars in the Marketing and Sales' fleet can be powered by either ethanol or petrol. The company also provides its drivers with training in "eco-driving" techniques, which encourages them to think ahead, planning acceleration and deceleration, anticipating traffic flow and maintaining a steady speed to improve fuel efficiency as well as safety. The company has set ambitious targets, which are being realised, e.g. the US Fleet Services are on track to achieving their goal to reduce greenhouse gas emissions from vehicles by 12% by 2010 (AstraZeneca 2008).

To fulfil demand, the product has to be distributed from the factory to the pharmacy. Only 10% of AstraZeneca's total greenhouse gas emissions come from freight transport, but nevertheless, improvements are being made. Bulk transport with final packing of products at the marketing companies has reduced demand for freight whilst simultaneously efforts have been made to use more environmentally friendly packaging options. For example, using slip-sheet techniques in air freight, rather than conventional pallets, reduces volume significantly and, wherever possible, reusable blankets have replaced polystyrene boxes for temperature-controlled transport. Selection criteria for road hauliers and airlines take into account both age and type of fleet as a matter of course. Trials are also underway into the use of container ships to replace some road and airfreight. This has the potential to reduce greenhouse gas emissions whilst simultaneously increasing security and providing more consistent storage conditions.

Finally, considerable efforts are going into the elimination of wastage in the distribution system. However, this is much more complicated than it sounds. Unlike most other commodities, it is essential for patient care that their medicine is always available from the pharmacy whenever they need it. However, demand for a particular medicine is variable and difficult to predict since it is derived from a very large number of pharmacies. In the past this problem was dealt with by ensuring that sufficient stocks were held by the manufacturer, distributer and pharmacy to meet all requirements. However, most pharmaceuticals have a limited shelf life and this policy resulted in very significant amounts of life expired medicines being continually returned to the manufacturer for destruction. This is both wasteful and very costly and serious attempts are now being made, using more sophisticated "lean" engineering and "just in time" delivery systems, to eliminate unnecessary stocks in the supply chain and thus reduce overall wastage whilst ensuring continuity of supply to the patient.

7.4 Product Use and Disposal

A key aspect of product stewardship is that responsibility does not end at the point of sale, but continues to the end of the life cycle. As a consequence it is important that the end users of the product, health professionals and patients, have access to information on its potential environmental impact.

Until recently, such information was not readily available. However in 2005 Stockholm County Council introduced, and made publically available, an environmental hazard classification scheme that covered ca. 30% of the medicines used

in Stockholm (Anon 2005). This has since been updated annually. At the same time the Swedish Association of the Pharmaceutical Industry (LIF) took the initiative to develop a voluntary environmental classification system for pharmaceuticals used in the whole of Sweden. The system was developed by LIF and a number of Swedish stakeholders (Anon 2007a, Mattson et al. 2007) in conjunction with expert representatives from international pharmaceutical companies. The resulting information is made available on the website of the Swedish Doctors Prescribing Guide (www.FASS.se/environment) and there is currently interest being expressed in extending the coverage across the European Union.

In theory, this information could be used by the doctor and the patient to ensure that the patient receives the most effective medication that produces the least environmental risk. However, in practice, after taking both efficacy and cost into account further treatment choices are likely to be very limited and in many cases the environmental profiles are likely to be similar. The data emerging from the LIF Classification scheme also shows that currently very few (<2%) of existing pharmaceuticals fall into the highest risk category. Consequently although classification schemes of this type provide a welcome improvement in transparency their environmental benefit is likely to be modest.

7.4.1 Unused Medicines

Although the majority of pharmaceuticals that are sold are used by patients, some are not, falling into the category of "unused or time expired" products. It is extremely difficult to produce any accurate information on the quantities of unused and time expired products (see Castensson and Ekedahl, Chap. 12 and Vollmer, Chap. 11, this book). For prescription only medicines, there are data on the amount of product that has been prescribed, but for "over the counter medicines" such information is not centrally collected. However, the amount of each drug that has not been used by the patient is unknown (and is probably unknowable with any accuracy). Medicines become unused for a variety of reasons; some prescribed drugs prove to be unsuitable and the treatment is abandoned, some patients are known to have a poor record at taking their medication, some patients rapidly recover whilst some patients die. In addition most individuals have a medicines cupboard containing "over the counter" analgesics such as paracetamol or aspirin, cough medicines and antiseptic creams. These almost invariably reach their expiry date before being completely utilised. Several recent attempts have been made to improve our estimates of the amount of unused and life expired medicines (Ruhoy and Daughton 2008) but it has to be remembered that there are likely to be major cultural differences between citizens in different countries in their approach to this issue.

Doctors have a role to play in minimising the amount of unused medicines. Needless to say, patients should only be prescribed pharmaceuticals when necessary and in appropriate amounts. In situations where the patient is likely to need

long term therapy, the efficacy of the relevant medicine should be established, using short term (7–14 days) prescriptions, before providing longer term (28 days) supplies. However, the desire to minimise unused medicines needs to be balanced by the much more important requirement to encourage patient adherence to their treatment. For example requiring patients on long term hypertension therapy to request a new prescription on a weekly basis would help to minimise the amount of unused medicines but would probably reduce the likelihood that the patient would take their medication continuously.

Historically one of the traditional disposal routes for such unused medicines was to flush them into the sewer. However, none of these "unused or time expired" medicines need to enter the environment since they can (and should) be returned to the pharmacist for disposal by incineration. Under the provisions of current European Union legislation (EC 2004), all EU Member States must establish collection schemes to recover and safely dispose of unused and expired medicines. The pharmaceutical industry is very supportive of these initiatives. A recent study by Taylor and Poulmaire (2008) showed that 20 of the EU Member States had now established take-back schemes for pharmaceuticals (see also Vollmer, Chap. 11, this book). Some of the schemes, particularly those in France and Sweden, were well established and successful. However, many of the more recent schemes did not appear, as yet, to be very effective. In the United States, pharmaceutical take-back schemes are difficult to organise due to serious conflicts that arise with legislation on the misuse of recreational drugs. However, all household refuse in the United States is either incinerated or disposed of in environmentally secure landfills. Thus advice from the regulators in the USA is to dispose of unused medicines in the household waste after ensuring that they cannot be reused (ONDCP 2007).

7.4.2 Excreted Medicines

Unlike many other products pharmaceuticals cannot be reused or recycled since the product is "consumed" by the patient under normal conditions and then excreted into the drainage system along with other bodily wastes. One aspect of stewardship is therefore to ensure that these excreted products exert minimal impact on the environment. Consequently all new medicines are evaluated during development for their potential environmental risk and this information is submitted to drug regulatory authorities as part of the application for drug authorisation approval[3].

The potential impact of a pharmaceutical on ecosystems is determined by two factors: effect and exposure, and the impact can be moderated by reducing either or both of these factors. The potential reduction in exposure has been discussed earlier (see Sect. 7.2.2) where a number of developments were described that should

[3] However, unlike the situation with veterinary pharmaceuticals, a human pharmaceutical cannot be denied marketing authorisation because of adverse environmental effects. The environmental authorities may, of course, use the data to impose strict discharge limits into the environment.

lead to the environmental residue per patient declining in the future. It must be recognised, however, that demographic changes mean that the number of patients undergoing therapy is likely to double by 2020 (PwC 2007). Individuals are living longer and economic improvement in the developing countries of the world is providing increasing access to medicines. Improvements in drug design may, or may not compensate for increased drug use but the safety margins between current environmental concentrations and effect levels are in general so large that an increase of 2–3× in drug release to the environment is unlikely to make any significant difference to the majority of environmental risk ratios.

The environmental impact of new drugs should also decline since drug designers are seeking to produce drugs with increasing specificity and very low non-target impacts. Of course, if the human receptor that the drug is designed to interact with is also found in other species in the environment there will always be the potential for the drug to promote a similar response. However, environmental concentrations are usually 10^5–10^6 times lower than the human therapeutic dose, which may ameliorate this.

Prior to the discovery of pharmaceutical residues in the environment, environmental risk assessment of new medicinal products had been somewhat rudimentary. The general assumption of academics, manufacturers, regulators, and health professionals had been that significant residues of pharmaceuticals were unlikely to be found in the environment because they were produced in relatively small quantities mostly below 100 tonnes per annum, they were unlikely to persist for long in the environment and would, in general, have to pass through wastewater treatment in order to get into the general environment. As a consequence the only regulatory requirements for environmental risk assessment were to measure some basic physicochemical properties and carry out some simple acute aquatic toxicity studies.

In the European Union, following the discovery of these pharmaceutical residues in the aquatic environment, the opportunity was taken during the revision (EC 2004) of the Community code relating to medicinal products for human use (EU Directive 2001/83/EC) to add a new clause requiring the *Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.* Subsequently, in 2007 the European Union introduced a sophisticated guidance document requiring a much more detailed and thorough assessment of environmental risk for the majority of new products[4] and for significant line extensions of existing ones (EMEA 2007a).

This is a three stage process leading to a tiered environmental risk assessment. The initial step (Phase 1) is a simple pre screening process to eliminate from further consideration those substances with an environmental concentration so low that they are considered to pose no significant risk. Any new pharmaceutical with a

[4] Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents.

predicted environmental concentration >10 ng/l, which in practice means the vast majority, goes forward into the second stage. This second stage (Phase 2, Tier A) is a screening risk assessment. Since all pharmaceuticals will enter the environment initially via water a series of aquatic ecotoxicological data are required. Experience has already shown that pharmaceuticals are very unlikely to exhibit acute effects at their predicted or measured environmental concentrations; consequently these ecotoxicological test data are aimed at determining chronic impacts. In addition, a set of basic physicochemical parameters are measured which enable the environmental compartments into which the pharmaceutical might be transported to be predicted. Based on the information generated in Tier A, a new pharmaceutical may proceed into Phase 2, Tier B where additional compartment specific information is required to categorise the overall environmental risk. Current experience suggests that most new pharmaceuticals will trigger some additional Tier B studies.

This guidance document had been developed over a 10 year period and some companies in 2007 were already going beyond the legal compliance requirements. Thus the major step change in requirements introduced by the new EMEA Guidance was not quite as dramatic as it might have seemed.

It was also explicitly stated in Clause 18 of the preamble to the revised Directive (EC 2004) that *In any event this impact should not constitute a criterion for refusal of a marketing authorisation.* This has been seen by many people as negating the requirement to undertake a risk assessment, i.e. why undertake a risk assessment if the risk is then ignored? However this is to misunderstand the situation. The revised directive recognises that society would be very concerned if a potentially life saving drug were to be refused authorisation solely on the basis that some environmental impact might occur as a consequence. However, the Directive does require that the environmental risk posed by any new medicine should be assessed and explicitly requires that if that assessment is adverse *specific arrangements to limit it shall be envisaged*. The EMEA Guidance document (EMEA 2007) is also quite explicit, stating that the environmental risk assessment report submitted as part of the application for marketing authorisation should contain *risk mitigation strategies as appropriate.*

In addition, EMEA is only providing a license to market the medicine. A range of other legal instruments, such as the EU Water Framework Directive (EC 2000) exist to control the subsequent release of this medicine into the environment.

7.4.3 Ecopharmacovigilance

It is inevitable that some small residues of some pharmaceuticals will continue to be found in the environment and, however comprehensive the risk assessment, we can never be absolutely certain that we understand every potential biological impact that these substances may have. It has therefore been suggested that an ecopharmacovigilance programme should be established in parallel to the pharmacovigilance programmes that exist for the identification of significant adverse

reactions in patients. Such a programme would have two objectives; firstly to evaluate risks to humans exposed to environmental residues and secondly to identify any environmental impacts that might be caused by such residues at an early stage. The first objective would probably require some post approval environmental monitoring in predicted "hot spots" to confirm the initial exposure assessments perhaps coupled with a broader assessment of human risks for vulnerable populations. The second objective might also at first sight seem plausible; however there are fundamental reasons why such an approach cannot work in practice.

A new medicine, when introduced into the market, will have been extensively studied and its impact will have already been evaluated both for efficacy and safety in several thousand patients. As a consequence, severe adverse reactions are only likely to appear at a very low frequency. However, despite the low frequency, absolute numbers of patients affected by an adverse reaction may still be high in view of the total size of patient populations. As a consequence the industry and WHO run comprehensive pharmacovigilance programmes to try to identify significant adverse reactions in patients as early as possible. Although the exposed population is well supervised and multiple exposures are unlikely the process is still not very efficient. Potential adverse effects are usually reported by patients themselves; in other words this is a reactive self monitoring process. Only a small proportion (1–10%) of adverse effects is thought to be reported by patients, and these are usually relatively acute in their nature and many of these signals of potential adverse effects turn out to be false positives.

Table 7.3 shows that there are significant differences between pharmacovigilance and ecopharmacovigilance.

This produces a large number of practical and insurmountable difficulties. Simply identifying a significant adverse reaction is an enormous challenge. In human pharmacovigilance the patient tells the health professional about the adverse reaction, in the environment adverse responses are only detected by external observation. There are >1.5 million species of plants and animals most of which are not being monitored. Even where monitoring is undertaken the signal to noise ratio means that only acute and severe responses have any chance of being detected within the very large variance caused by natural variability, disease, climate and predation.

Table 7.3 Differences between pharmacovigilance and ecopharmacovigilance

Parameter	Pharmacovigilance	Ecopharmacovigilance
Target	Restricted to a small identifiable number of a single well characterised species	Unrestricted: potentially all species in all environments
Exposure	Accurately known since it is defined by the therapeutic regime	Regional average is predictable but actual exposure is unknown
Observation	Exposed population under regular expert supervision	Exposed populations monitored irregularly if at all
Confounding factors	Can usually be identified by discussion with patient	A potentially very large and unknown number

This is even more problematic in the case of pharmaceuticals where the concentrations in the environment are much too low to trigger any acute responses and where any species might be the "most sensitive".

Even if a significant adverse reaction can be differentiated from the noise, trying to identify the cause of this effect poses another enormous challenge. There are >30,000 synthetic chemicals in use and many of these are potentially present in the environment at similar, or higher, concentrations to pharmaceuticals. In addition, species in the environment are exposed to multiple and variable stressors. Establishing any ecopharmacovigilance programme to watch for potential chronic impacts of pharmaceuticals on ecosystems thus appears to be an impossible objective.

However, environmental signals have previously been used to identify problems caused by human exploitation of synthetic substances, e.g. the impact of TBTO in antifouling paints on marine invertebrates, the impact of Diclofenac on the Asian vulture population and the impact of natural and synthetic steroids on the feminisation of male freshwater fish. Thus a generalised ecovigilance reporting system, which could receive information on adverse environmental responses from any of the current global multiplicity of environmental monitoring programmes, could undertake a valuable alerting function. The United Nations Environmental Programme or the European Environment Agency might appropriately take the lead on such a system.

7.5 Conclusions – Reducing the Uncertainties

In the last 20 years since Richardson and Bowron (1985) produced their seminal publication, we have learnt a great deal about the potential impact of pharmaceutical residues in the environment. We recognise that many pharmaceuticals can be found at ng/l concentrations in the environment (with some at concentrations in the low μg/l), primarily as a direct consequence of therapeutic use by patients leading to constant input from multiple sources. The impact on human health appears to be insignificant, as does the acute impact on ecosystems. At present long term impacts on ecosystems caused by some pharmaceuticals cannot be ruled out, although increasingly the evidence from chronic studies does not indicate that these are widespread (Boxall et al. 2008).

Nevertheless the research pharmaceutical companies take their stewardship responsibilities seriously and are continuing to pursue research to reduce the uncertainties further. There are a number of areas where further investigations would be helpful, as described below.

A very large amount of information on pharmacokinetics and mammalian toxicology is produced during the development of any new medicine. Initial studies (Owen et al. 2007) have shown that such information could be valuable in developing intelligent ecological testing strategies but much more work is needed to investigate and validate this approach.

It is known that some pharmaceuticals are removed from wastewater by biological treatment plants; some are partially removed whilst others pass straight through. However, it is not known whether the pharmaceuticals are degraded or simply adsorbed onto the sewage sludge and, if the latter is the dominant mechanism, whether the adsorbed material can be desorbed. It has also been observed that removal efficiencies can vary dramatically, even with the same plant configuration, which raises the question as to whether all existing biological treatment plants could be tuned for maximum removal efficiency.

Most pharmaceutical compounds are not "readily degradable" but few of them could be classified as completely persistent. Most of them appear to degrade slowly in the environment via a variety of biotic and abiotic mechanisms. Further studies in this area, especially if the mechanism could be linked to structure, would enable improved prediction of actual environmental concentrations to be undertaken and could potentially provide valuable information during the lead identification and optimisation stages in drug design.

References

Alder AC, Bruchet A, Carballa MC, Clara M, Joss A, Löffler CS, McArdell KM, Miksch K, Omil F, Tuhkanen T, Ternes T (2006) Consumption & occurrence. In: Ternes T and Joss A (eds.) Human Pharmaceuticals, Hormones and Fragrances – The Challenge of Micropollutants in Urban Water Management. IWA Publishing, London, pp. 15–54

Anastas PT, Warner JC (1998) Green Chemistry: Theory and Practice. Oxford University Press, Oxford

Anon (2005) Environmentally Classified Pharmaceuticals. Stockholm County Council

Anon (2007a) Environmental classification of pharmaceuticals in www.fass.se : guidance for pharmaceutical companies, January 2007. Swedish Association of the Pharmaceutical Industry Stockholm

Anon (2007b) Product Stewardship Institute Web: http://www.productstewardship.us/display-common.cfm?an=1&subarticlenbr=55

AstraZeneca (2008) Responsibility – Climate Change. Web: http://www.astrazeneca.com

Boxall A, Brooks B, Backhaus T, Gouy D, Hickman S, Kidd K, Metcalfe C, Monteiro S, Netherton M, Parrot J, Smith E, Straub JO, Weeks J (2008) Ecotoxicology of pharmaceuticals: Making sense of the published literature. EU Framework 6 Project KNAPPE Deliverable number: D4.1. Report of the WP4 Workshop; 28–31 January, 2008, Harrogate, UK

BristolMyers Squibb (2007) Land Use & Biodiversity. Web: http://www.bms.com/ehs/perfor/data/landus.html

Clarke J, Summerton L (2010) Challenges and opportunities for incorporating green chemistry into drug design to minimise environmental impact. (In press)

Crow JM (2008) Pharma goes green to cut costs. Chemistry World, July 2008

Cunningham VL, Buzby M, Hutchinson TH, Mastrocco F, Parke N, Roden N (2006) Effects of human pharmaceuticals on aquatic life: Next steps. Environ Sci Technol 40, 3457–3462

Curzons AD, Constable DC, Cunningham VL (1999) Solvent selection guide: A guide to the integration of environmental, health and safety criteria into the selection of solvents. Clean Products Process 1, 82–90

Daughton CG (2003) Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health Part I: Rationale for and avenues towards a green pharmacy. Environ Health Perspect, May 2003

Dunn P, Wells A, Williams MT (2010) Green Chemistry in the Pharmaceutical Industry. Wiley, Germany

EC (2000) Directive 2000/60/ec of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. Official Journal L327 22/12/2000: 1–72

EC (2004) Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal L136 30/04/2004: 34–57

EMEA (2007) Guideline on the environmental risk assessment of medicinal products for human use. European medicines Evaluation Agency Guidance Note EMEA/CHMP/SWP/4447/00. Web: http://www.emea.europa.eu/pdfs/human/swp/444700en.pdf

EPA (2008) Presidential Green Chemistry Challenge 2008. Web: http://www.epa.gov/gcc/pubs/pgcc/presgcc.html

GlaxoSmithKline (2007) Answering the questions that matter. Corporate Responsibility Report 2007. Web: http://www.gsk.com/reportsandpublications.htm

Halling-Sørensen B, Nielsen SN, Lanzky PF, Ingerslev F, Holten-Lützhøft HC, Jørgensen SE (1998) Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment: A Review. Chemosphere 36, 357–393

IFPMA (2008) Web: http://www.ifpma.org/index.php?id=600

Kümmerer K (ed.) (2004) Pharmaceuticals in the Environment. 2nd edition, Springer-Verlag, New York

Kümmerer K (2007) Sustainable from the very beginning: rational design of molecules by lifecycle engineering as an important approach for green pharmacy and green chemistry. Green Chem 9, 899–907

Kümmerer K, Al-Ahmad A, Bertram B, Wießler M (2000) Biodegradability of antineoplastic compounds in screening tests: Influence of glucosidation and of stereochemistry. Chemosphere 40, 767–773

Larsson DGL, de Pedro C, Paxeus N (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Hazard Mater 148(3), 751–755

Mattson B, Näsman I, Ström J (2007) Sweden's voluntary drug environmental classification system. RAJ Pharma, 153–158

ONDCP (2007) Proper Disposal of Prescription Drugs. US Office of National Drug Control Policy, Washington, DC. Web: http://www.whitehousedrugpolicy.gov/

Owen SF, Giltrow E, Huggett DB, Hutchinson TH, Saye J, Winter MJ, Sumpter JP (2007) Review: Comparative physiology, pharmacology and toxicology of ß-blockers: Mammals versus fish. Aquat Toxicol 82, 145–162

Pfizer (2007) Water Use & Conservation. Web: http://www.pfizer.com/responsibility/ehs/ conserving_water_performance.jsp

PwC (2007) Pharma 2020: The Vision. Which Path Will You Take? PriceWaterHouse Coopers, London

Ramessar K, Capell T, Christou P (2008) Molecular pharming in cereal crops. Phytochem Rev 7, 579–592

Richardson ML, Bowron JM (1985) The fate of pharmaceutical chemicals in the aquatic environment. J Pharm Pharmacol 37, 1–12

Ruhoy IS, Daughton CG (2008) Beyond the medicine cabinet: An analysis of why & where medications accumulate. Environ Int 34, 1157–1169

Sheldon RA (1994) Consider the Environmental Quotient. Chemtech 24, 38–47

Stan HJ, Heberer T, Linkerhägner M (1994) Occurrence of clofibric acid in the aquatic system – does the medical application cause contamination of surface, ground and drinking water? Vom Wasser 83, 57–68

Taylor D, Poulmaire M (2008) An initial survey of unused & expired medicine take-back schemes in the European Union. Poster Presentation Pharmaceutical Products in the Environment: Towards Lowering Occurrence and Impact KNAPPE International Conference. Nimes (France)

Thomas KV, Dye C, Schlabach M, Langford KH (2007) Source to sink tracking of selected human pharmaceuticals from two Oslo city hospitals and a wastewater treatment works. J Environ Monit 9, 1410–1418

United Nations (2002) Convention on the Conservation of Biological Diversity. Web: http://www.biodiv.org/convention/default.shtml

Chapter 8
Protein and Peptide Therapeuticals: An Example of "Benign by Nature" Active Pharmaceutical Ingredients

Jürg Oliver Straub

8.1 Introduction

Protein and peptide therapeuticals (PPTs) form a relatively recent class of active pharmaceutical ingredients (APIs) (Leader et al. 2008). Mostly, they consist of biotechnologically produced monoclonal antibodies and peptide hormones, but there are also examples isolated from natural tissues, as well as some chemically synthesised peptides. The monoclonal antibodies in particular are highly specific and therefore constitute precisely targeted APIs. In certain cases these PPTs may be covalently bound to long-chained polyethylene glycol (PEG) as so-called PEGylated PPTs, which show significantly prolonged elimination half-lives (Webster et al. 2007).

The European Medicines Evaluation Agency (EMEA) guideline on environmental risk assessment (ERA) for human pharmaceuticals (EMEA 2006) contains a categorical exclusion clause, whereby vitamins, proteins, peptides, electrolytes, carbohydrates, lipids, vaccines and herbal medicines are exempt from environmental risk assessment. Intuitively, this makes perfect sense. However, the fact that there is a number of highly toxic natural proteins calls for caution. These are widely distributed, from bacteria (e.g. botulinum, clostridium or tetanus toxins; Alouf and Popoff 2005) to plants (e.g. ricin, phasin; Frohne and Pfänder 2005) and animals (e.g. certain snake venoms or amphibian toxins; Mebs 2002). On the other hand, more and more PPTs are being developed or are already on the market as APIs (Leader et al. 2008). They range from biotechnologically produced compounds, e.g. recombinant hormones, monoclonal antibodies or botulinum toxin (Allergan 2007), to wholly chemically synthesised peptides. In view of this uncertainty, various PPTs were tested in standard assays, to substantiate or refute their presumed environmental compatibility.

J.O. Straub (✉)
Corporate Safety, Health and Environmental Protection Department, F. Hoffmann-La Roche Ltd, CH–4070, Basle, Switzerland
e-mail: juerg.straub@roche.com

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_8,

8.2 Materials and Methods

8.2.1 Substances Tested

Tests were performed with the following eight PPTs, all from F. Hoffmann-La Roche Ltd. One recombinant hormone (Neorecormon®, Epoetin-β, *M*∼37,000 g/mol), three recombinant monoclonal antibodies (Actemra®, Tocilizumab, *M*∼150,000 g/mol; Avastin®, Bevacizumab, *M*∼150,000 g/mol; one monoclonal antibody in development, named here MAbDevl, *M*∼150,000 g/mol), a synthetic 36-amino-acid peptide (Fuzeon®, Enfuvirtide, *M*∼4,500 g/mol), a synthetic 30-amino-acid peptide in development (dubbed here S30AAPPT, *M*∼3,300 g/mol) and two PPTs covalently bound to a long-chain PEG (Pegasys®, PEGylated interferon–α-2a, *M* ∼60,000 g/mol; Mircera®, PEGylated epoetin-β, *M*∼60,000 g/mol). Safety data sheets for most of these PPTs, with the exception of the development products, are available from the Roche Internet website (http://www.roche.com/corporate_responsibility/environment/safety_data_sheets.htm)

8.2.2 Tests Performed

The eight PPTs were tested at different contract laboratories in standard biological degradation and acute environmental toxicity assays according to Organisation for Economic Co-Operation and Development (OECD) guidelines, under Good Laboratory Practice (GLP) or International Standardisation Organisation/International Electrotechnical Commission (ISO/IEC) 17025 quality assurance. The assays included a ready biodegradability test registering mineralisation (Manometric Respirometry Test, OECD Test Guideline 301F; or Closed Bottle Test, OECD TG 301D; OECD 1992a) on the environmental fate side as well as algal growth inhibition (OECD TG 201; OECD 2006), acute daphnid immobilisation (OECD TG 202; OECD 2004) or acute fish toxicity (OECD TG 203; OECD 1992b) on the effects side. Mostly, the tests were performed with formulated APIs, in every instance fully conforming to specifications and within the use-by date. In these cases, the concentration stated refers to the API only and, especially for the biodegradation tests, properties of the excipients such as theoretical, biochemical or chemical oxygen demand (ThOD, BOD or COD, respectively), or biodegradability if applicable, were taken into account.

8.2.3 Results

8.2.3.1 Biodegradability

The tests resulted in unambiguous ready biodegradability for six of the eight PPTs, namely the four pure proteins as well as the synthetic peptides Fuzeon and

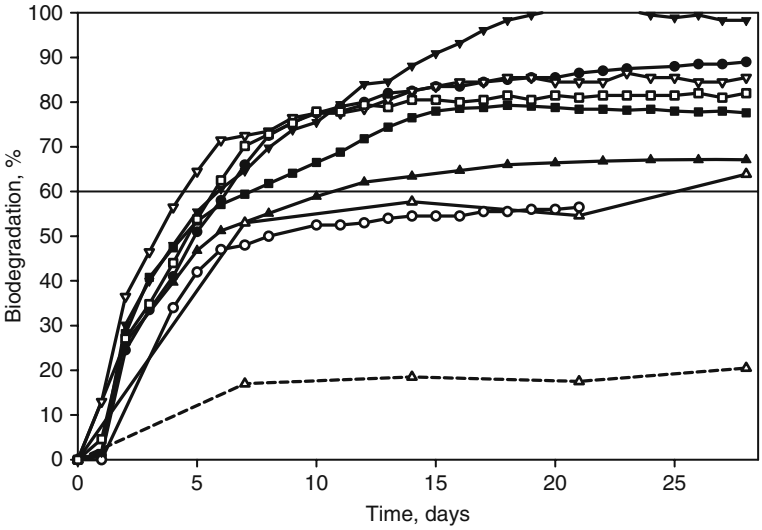


Fig. 8.1 Ready biodegradability tests with the eight protein and peptide therapeuticals. Biodegradability, i.e. mineralisation in terms of biochemical oxygen demand (BOD) vs. theoretical oxygen demand including nitrification ($ThOD_{NO3}$) or vs. chemical oxygen demand (COD), is shown in per cent. The horizontal line at 60% biodegradation is the threshold for ready biodegradability in tests measuring BOD. Symbols: *filled circles* Actemra; *filled squares* Avastin; *filled triangles* Fuzeon; *inverted filled triangles* MAbDevl; *open circles* Mircera; *open squares* Neorecormon; *open triangles* Pegasys; *inverted open triangles* S30AAPPT. For Pegasys (*open triangles*), BOD/COD for the whole molecule is given as a *dashed line*, while the $BOD/ThOD_{NO3}$ calculated for the protein moiety only is shown as a *solid line*

S30AAPPT (Fig. 8.1). In all six cases there was a rapid increase in BOD from day 1, implying a very short, insignificant lag phase. The ready biodegradability threshold of 60% $BOD/ThOD_{NO3}$ (ThOD including the oxygen demand for full nitrification of these nitrogen-rich compounds) was attained between days 5 and 11, and even the "slowest" pure protein met the 10-day-window criterion (OECD 1992a). A plateau was reached in all cases between days 10 and 16.

The PEGylated interferon Pegasys showed poor biodegradability (Fig. 8.1, dashed line) in a Closed Bottle Test with very low inoculum concentration and high substance concentration, due to the need for a strong signal in terms of dissolved oxygen depletion. As PEGs degrade more slowly the longer their chain length is (Watson and Jones 1977, Clariant 2002), the observed BOD was related to the $ThOD_{NO3}$ for the protein moiety only (which makes up approximately one-third of the mass of the whole Pegasys molecule), resulting in the solid Pegasys line in Fig. 8.1. In spite of this correction for slow degradability of the PEG moiety, full ready biodegradability matching the 10-day-window criterion was still not reached for the protein moiety in this suboptimal assay. Nevertheless, it does suggest substantial biodegradation of the interferon moiety. Moreover, the BOD evolution pattern is comparable to the unPEGylated PPTs, if somewhat reduced.

A similar degradation curve resulted for the total PEGylated epoetin Mircera, which has approximately twice the relative protein content compared with Pegasys. Specific analysis showed rapid disappearance of total Mircera within only 4 days, while on day 21 over 70% of the PEG fraction was still detected, again substantiating rapid biodegradation of the protein moiety. The Mircera test was stopped after 21 days, when the total BOD/$ThOD_{NO3}$ for both the PEG and protein moieties was at approximately 56%. Linear extrapolation of the degradation curve to 28 days would just break the 60% line, attaining ready biodegradability for the whole compound; alternatively, re-calculating the BOD for the $ThOD_{NO3}$ of the protein moiety only would bring the degradation percentage above 70% at day 21 (not shown).

8.2.3.2 Ecotoxicity

None of the seven PPTs tested in a Manometric Respirometry Test (OECD TG 301F) nor Pegasys in a Closed Bottle Test (OECD TG 301D) showed any inhibitory effect against the activated sludge bacteria in the toxicity controls of the ready biodegradability tests. Hence, there are eight bacterial no-observed-effect concentrations (NOECs), all at the only tested concentration of the PPTs (Table 8.1).

For the acute ecotoxicity test battery with the 3 standard organisms algae, daphnia and fish, 18 results are available for the eight compounds (Table 8.1). With three exceptions, all NOECs are $\geq$100 mg API/l nominal concentration, the respective highest tested concentration. One of the exceptions is Avastin, with an algal NOEC of approximately 80 mg API/l. In this particular test, the formulated Avastin solution

Table 8.1 Protein and peptide therapeuticals (PPT) ecotoxicity dataset (chronic for green algae and activated sludge bacteria, acute for daphnia and fish)

	NOEC (mg API/l, nominal concentration) for			
PPTs	Algae	Daphnia	Fish	Activated sludge bacteria[a]
Actemra	100	100	100	100
Avastin	~80[b]	100	ND	100
Fuzeon	100	ND	ND	100
MAbDevl	100	100	<100[b,c]	50
Mircera	200	200	200	100
Neorecormon	100	100	ND	100
Pegasys	ND	300	300	800
S30AAPPT	6.3[b]	200	ND	25

API: Active pharmaceutical ingredient; ND: Not determined; NOEC: No-observed-effect concentration.

[a] From the inhibition/toxicity controls of the ready biodegradability studies, referring to the only tested concentrations.

[b] See discussion of these values in the results.

[c] Behavioural effects noted, but no lethality observed at 100 mg MAbDevl/l nominal concentration.

produced turbidity in the algal medium, which was judged by the study director to be the reason for the slightly decreased growth. Hence, the moderate inhibition most probably is not caused by actual toxicity of Avastin but rather by physical shading that reduced the light available for the algae.

Slight turbidity was also noted for MAbDevl, but this had no effect on algal growth at 100 mg/l nominal. However, in the fish limit test at 100 mg API/l nominal concentration, turbidity from 24 h into the test coincided with the onset of hypoactivity, straightened or constricted tail fins as well as swimming close together, often near the surface. This behaviour is consistent with stress reactions and the study director suggested stress due to the turbidity and visible precipitates as the cause of the observed effects. Hence, while there was a behavioural effect at 100 mg API/l nominal (i.e. NOEC <100 mg API/l), there was no lethality at this nominal concentration (zero lethality concentration, $LC_0 = 100$ mg API/l).

The third exception is S30AAPPT, which showed an algal NOEC of 6.3 mg active ingredient/l nominal concentration. At first sight, particularly in comparison with the other PPTs, this is an astonishingly low value. However, the 50% effect concentration for yield (EyC_{50}) was 52.1 mg/l and the 50% effect concentration for growth rate (ErC_{50}) was >200 mg/l, the highest tested concentration in this case (data not shown). This suggests that the slope of the dose–response curve is rather flat. Indeed, the growth rate NOEC over the first 24 h of the test was 200 mg/l, while over the first 48 h it dropped to 20 mg/l and over the whole duration of 72 h to 6.3 mg/l. However, the percentage inhibition of the growth rate at 72 h was 15% at 20 mg/l, 13.3% at 63 mg/l and finally 17.6% at 200 mg/l. Hence, while S30AAPPT did show a statistically significant growth rate inhibition at a concentration of 20 mg/l (LOEC, lowest observed effect concentration), this inhibition was not very strong, moreover, it was barely stronger at 63 and at 200 mg/l, but always below 20% inhibition. The stronger decline in yield is a consequence of the diminished growth rate and the integrating property over time of the yield endpoint (e.g. Eberius et al. 2002). Also, the algal NOEC is basically a chronic endpoint, in contrast to the acute daphnid and fish NOECs. Hence, a minor toxicity of S30AAPPT towards algae is acknowledged, but the observed inhibition is not very strong, particularly not as strong as the NOEC would suggest on its own.

8.3 Discussion

All of the PPTs tested here are not bioavailable to patients by oral administration as they would be broken down by proteolytic catabolism before reaching the blood-stream (Leader et al. 2008). For this reason they are also not toxic by oral administration (F. Hoffmann-La Roche Ltd, Basle, internal substance documentation, unpublished). Also, when administered by injection, they are extensively metabolised and eventually excreted mainly as non-recognisable and non-functional fragments. Due to this protein breakdown in patients, the initial environmental exposure to these active ingredients is very low.

Out of the eight PPTs, four biotechnologically produced proteins, two other such proteins covalently bound to a long PEG chain and two synthetic peptides, six attained full ready biodegradability. The two PEGylated compounds are judged to have reached the biodegradation pass level, at least for the active protein moiety, but both failed the 10-day-window criterion. PEGylation has been specifically developed for medical applications because it strongly extends the human elimination half-life, delaying both enzymatic metabolisation and urinary excretion. Thereby, PEGylation increases the therapeutical efficacy, respectively the period between applications (Webster et al. 2007). A similar retardation may reasonably be expected for the microbial degradation of PEGylated compounds, too, particularly when the PEG moiety has approximately twice the mass of the protein moiety, as is the case for Pegasys. Moreover, none of the active ingredients or total formulations caused any inhibition of activated sludge bacteria in the biodegradation toxicity controls. Hence, very high to good biodegradation is expected in sewage works and, in particular, no toxic hazard to wastewater treatment is assumed.

The available acute ecotoxicity data suggest no excess toxicity from the eight PPTs tested, both for algae (seven tests), daphnia (seven tests) and fish (four tests). In view of lacking oral bioavailability in human patients, four fish tests were judged to be sufficient as proof of concept. One slightly lower algal NOEC was most probably caused by reduced light availability due to turbidity. A second showed algal toxicity, with a low NOEC but a flat dose-response curve and consistently less than 20% growth rate inhibition. Still, even an algal NOEC of 6.3 mg/l would not be termed very highly toxic. One formulated PPT caused behavioural effects in fish consistent with stress reactions, probably caused by precipitates, at the only tested concentration of 100 mg API/l. Hence, in view of the concentrations applied and of the effects seen (if any), there is no or only very much minor concern regarding the ecotoxicity of the PPTs tested. Moreover, algae seem to be the most sensitive organisms in this set of tests with PPTs, which is comparable to findings for regular, non-PPT APIs, where algae or daphnia were the most sensitive in 80% of cases (Hutchinson et al. 2003).

8.4 Conclusion

"Biological", protein and peptide, APIs have a very low excretion rate as such due to extensive metabolism. Ready biodegradability and acute ecotoxicity studies with several PPTs suggest rapid biodegradation in sewage works and surface waters, beside indicating a low ecotoxic potential. Hence, these active substances are judged to present no significant risk to sewage works and surface waters. In view of these characteristics, PPTs may be termed "benign by nature", and thus they constitute environmentally sustainable compounds. Moreover, regarding the human pharmaceuticals environmental risk assessment, the categorical exclusion (EMEA 2006) of such PPTs seems well justified.

Acknowledgment The laboratory technicians and study directors at BMG Engineering Ltd (Switzerland), IBACON GmbH (Germany), NOTOX B.V. (The Netherlands), Harlan/RCC Ltd and SOLVIAS (both Switzerland) are acknowledged for performing competent environmental fate and toxicity studies.

References

Allergan (2007) BOTOX® (Botulinum Toxin Type A); http://www.allergan.com/site/products/consumers/home.asp?id =botox, accessed 7 March 2008

Alouf JE, Popoff MR (eds.) (2005) The Comprehensive Sourcebook of Bacterial Protein Toxins. 3rd edition, Academic Press, New York

Clariant (2002) Safety data sheet for Polyglycol 6000P, 27.02.2002. Clariant Ltd, Basle, Switzerland

Eberius M, Mennicken G, Reuter I, Vandenhirtz J (2002) Sensitivity of different growth inhibition tests – just a question of mathematical calculation? Theory and practice for algae and duckweed. Ecotoxicology 11, 293–297

EMEA (2006) Note for Guidance on Environmental Risk Assessment of Medicinal Products for Human Use. CPMP/SWP/4447/00. EMEA, London; http://www.emea.eu.int/pdfs/human/swp/444700en.pdf, accessed 7 March 2008

Frohne D, Pfänder HJ (2005) Poisonous Plants. 2nd edition, Blackwell, Oxford, UK

Hutchinson TH, Barrett S, Buzby M, Constable D, Hartmann A, Hayes E, Huggett D, Länge R, Lillicrap AD, Straub JO, Thompson RS (2003) A strategy to reduce the numbers of fish used in acute ecotoxicity testing of pharmaceuticals. Environ Toxicol Chem 22, 3031–3036

Leader B, Baca QJ, Golan DE (2008) Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discov 7, 21–39

Mebs D (2002) Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists. Medpharm, Stuttgart, Germany

OECD (1992a) OECD Guideline for Testing of Chemicals, Test no. 301, adopted by the Council on 17th July 1992: Ready Biodegradability. OECD, Paris, France

OECD (1992b) OECD Guideline for Testing of Chemicals, Test no. 203, adopted by the Council on 17th July 1992: Fish, Acute Toxicity Test. OECD, Paris, France

OECD (2004) OECD Guideline for Testing of Chemicals, Test no. 202, adopted by the Council on 13th April 2004: *Daphnia* sp. Acute Immobilisation Test. OECD, Paris, France

OECD (2006) OECD Guideline for Testing of Chemicals, Test no. 201, adopted by the Council on 23rd March 2006: Freshwater Alga and Cyanobacteria, Growth Inhibition Test. OECD, Paris, France

Watson GK, Jones N (1977) The biodegradation of polyethylene glycols by sewage bacteria. Water Res 11, 95–100

Webster R, Didier E, Harris P, Siegel N, Stadler J, Tilbury L, Smith D (2007) PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. Drug Metab Dispos 35, 9–16

Chapter 9
Rational Design of Molecules by Life Cycle Engineering

Klaus Kümmerer

9.1 Introduction

The history of pharmaceutical sciences is an impressive success story. The products of the pharmaceutical industry help to maintain the modern way of living, and contribute to our high living standard and health. Today, proper and effective treatment of emissions and prevention of emissions into air, water and soil is in practice in developed countries and will hopefully day become commonplace around the world. It has been known since the turn of the twentieth century that pharmaceutical products themselves cause environmental pollution and that they may, due to their very nature, present a health risk for the consumer. These molecules end up in the environment, not because of improper use, but, paradoxically, because of proper use. The first publications on the presence of pharmaceuticals in the environment appeared in the early seventies of the last century, but it wasn't until the advent of better analytical instruments in the 1990s that this topic gained more and more interest among scientists, and also aroused interest in the general public. Today, the presence of pharmaceuticals in the environment is a widely accepted fact; however, we are now having to deal with the possible effects of the compounds on wildlife such as fish, dahnids, bacteria, etc. People have started to be concerned about the presence of pharmaceuticals in their drinking water.

In most cases information on the long term risks of active pharmaceutical ingredients is missing, while the acute effects are quite comprehensively documented. Data allowing for a sound risk assessment of metabolites and transformation products are more or less completely missing. Furthermore, up to now, risk assessments have been undertaken for single substances only and not for mixtures. Some of the active pharmaceutical ingredients, so called CMR-compounds, have *c*arcinogenic, *m*utagenic or *r*eproductive toxic effects. It is unclear how such compounds should be assessed. Besides toxicity, the issue of persistence is of particular importance for the

K. Kümmerer (✉)
Department of Environmental Health Sciences, University Medical Center Freiburg,
Breisacherstraße 115b, D-79106 Freiburg, Germany
e-mail: klaus.kuemmerer@uniklinik-freiburg.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_9,

assessment of the environmental significance of substances. Persistent organic pollutants increase the potential for long-term and, hence, varied effects. The longer the exposure, the greater the risk becomes for multiple contamination of the ecosystem. This cannot be tested in advance with the presently available test systems (Cairns and Mount 1990). There are three approaches to risk reduction, i.e. to reducing the input of pharmaceuticals into the environment (Kümmerer 2007, Keil, Chap. 15, this book):

Firstly, a major unknown with respect to drugs as pollutants is what fractions of drug residues occurring in the ambient environment result from discarding leftover drugs (Götz and Keil 2007, Daughton and Ruhoy, Chap. 6, this book, Götz and Deffner, Chap. 10, this book, Castensson and Ekedahl, Chap. 12, this book, Vollmer, Chap. 11, this book). Informing doctors, pharmacists and patients properly could contribute to reducing the input of active pharmaceutical ingredients into the aquatic environment.

Secondly, the strategy for risk reduction that has been most extensively discussed within recent years is advanced effluent treatment. Advanced treatment of effluents has been investigated using photochemical oxidation processes (e.g. Watkinson et al. 2007, Strässle 2007, Isidori et al. 2007), filtration (Drewes et al. 2002, Heberer and Feldmann 2005), application of powdered charcoal (Metzger et al. 2005, Nowotny et al. 2007), constructed wetlands (Matamoros and Bayona 2006) and ultrasonic treatment in the presence of oxidizing agents (Naddeo et al. 2009). Reviews on the advantages and disadvantages of the different technologies are available (Schulte-Oehlmann et al. 2007, Jones et al. 2007, Wenzel et al. 2008, Ternes and Joss 2006, www.start-project.de). It has been found that each type of advanced effluent treatment has its specific limitations and in general some severe drawbacks. The following main limitations and disadvantages can be identified for advanced effluent treatment (Kümmerer 2008).

- Efficiency may depend strongly on the type of compound. For example, for photolysis the presence of a suitable chromophore is a must. Ozone only reacts with certain compounds containing carbon-carbon double bonds. Sorption to activated charcoal depends on polarity and electronic properties of the molecule to be sorbed. It has been learned that none of the technologies can remove all of the compounds (Qiting and Xiheng 1988, Ravina et al. 2002, Schröder 2002, Wenzel et al. 2008, Méndez-Arriaga et al. 2008, Calza et al. 2008, Rizzo et al. 2009, Naddeo et al. 2009, Vasconcelos et al. 2009a, b). Will the current advanced treatment work for new compounds of the future?
- Mutagenic and other toxic properties have been found for reaction products of (photo) oxidation processes (Isidori et al. 2005, 2007, Lee et al. 2007, Wei-Hsiang and Young 2008, Méndez-Arriaga et al. 2008, Calza et al. 2008, Rizzo et al. 2009, Naddeo et al. 2009).
- Prolongation of the treatment time in sewage treatment plants results in little improvement of elimination rates High costs may ensue because of the need to enlarge the sewage treatment plants.

- Combined sewer overflow (10–30% of the total water flow) in case of storm water will not be treated.
- Sewage that has infiltrated the ground before it reaches sewage treatment plants due to leaking sewage pipes is not treated.
- In the case of antimicrobials: Is resistance in bio-membrane reactors due to enrichment of antibiotics and resistant bacteria increasing? Resistant bacteria and the genetic material encoding resistance are not fully retained by membranes in case of membrane based reactors.
- Advanced treatment processes depend on a high energy input and minimum water flow. Therefore, they will not be applicable in arid and poor countries.
- Additional energy demand causes additional emissions of CO_2 (Jones et al. 2007) and will as a green house gas cause additional costs for consumers and companies[1] as well as for the general public in the future.
- The costs are often unclear and it is often not known whether they are affordable. Different authors present different data regarding cost, depending on the assumptions made. It is not yet clear whether the additional costs are acceptable (Dohmann 2004, Jones et al. 2007).

In summary, advanced effluent treatment should not be considered as a general solution to the problem, but as part of the solution on a case by case basis. Advanced treatment processes are not compatible with sustainable development because they are end of the pipe technologies that are not affordable in all countries and costly for manufacturers. Wenzel et al. (2008) investigated the advantages and disadvantages of advanced waste water treatment for the improved removal of micro-pollutants using environmental life cycle assessment (LCA) and a published literature review of advanced treatment performance. The authors determined the "environmental break-even" point where the removal of micro-pollutants and reduction in (eco-) toxicity will outweigh increased resource- and energy consumption. In some of the studied scenarios it was found that more environmental impact may be induced than removed by advanced treatment (i.e., the break-even point is not reached!?) Therefore, other approaches are necessary.

Thirdly, given the poor prognosis for end-of-pipe technologies and the fact that pharmaceuticals that are properly consumed end up in waste water and that they cannot be covered by the first approach, it is advantageous to shift our focus to "the beginning of the pipe", i.e. the molecules themselves. With the advent of green and sustainable chemistry, it has been learned that it is necessary to keep in mind the whole life cycle of products and molecules (Anastas and Warner 1998, Clark and Smith 2005, Clark 2006). This is addressed by the concepts of green and sustainable

[1] See for example the Kyoto-Protocol (http://ec.europa.eu/environment/climat/kyoto.htm) and the European Union Emission Trading System (EU ETS, EU 2003). In January 2008, the European Commission proposed a number of changes to the scheme, including inclusion of other greenhouse gases, such as nitrous oxide and perfluorocarbons. It is also under consideration whether or not to extend the EU ETS to other industries. Other drivers for green chemistry have been described by Clark (2006).

chemistry and more recently by the concept of green and sustainable[2] pharmacy (see Chap. 1).

The third strategy ("green" pharmaceuticals) is emerging from the field of green chemistry: An important building block within green and sustainable pharmacy is the concept benign by design. In terms of sustainability it seems to be the most promising in the long run. In general, a suitable combination of the three management strategies is likely to be the most effective in mitigating the risks presented by pharmaceuticals.

9.2 Benign by Design

9.2.1 Safe and Sustainable Molecules

Because of the ever improving sensitivity of analytical instruments it has become clear that despite all measures to prevent pollution of the environment by chemicals, chemical contaminants are still present in the environment, sometimes only in low concentrations (typically ng/L to μg/L-range; micro-pollutants"), and that they are also ubiquitous. Therefore, according to the principles of green chemistry, the functionality of a chemical should not only include the properties necessary for its application, but also easy and fast degradability after use. Taking into account the full life cycle of pharmaceuticals will lead to a different understanding of the necessary functionality (Kümmerer 2007, 2010).

In current discussions, improvements in synthesis are very prominent, whereas the environmental properties of the molecules are rather not recorded enough attention. Applying the principles and knowledge of green chemistry to pharmaceuticals is a necessary future step. It means that easy degradability after use or application is taken into account even before a pharmaceutical is synthesised. Environmental properties can be included in the same way pharmaceutical lead structures are optimized with respect to their pharmacokinetic and pharmacodynamic profile. In this case, the resulting molecules are "benign by design". It is clear that an inclusion of this type must take place at the very early stages of drug development. It is not suitable for a compound that has already been improved and tested with regards to its medical properties and is perhaps shortly to undergo licensing. The benign by design approach is not completely new. It is also under discussion for chemicals in general (Boethling et al. 2007, Kümmerer 2007).

Pharmaceuticals that fulfil their medical needs and are not toxic are intrinsically safe. This is one of the core concepts of the development and application

[2] "Green" and "sustainable" are sometimes used synonymously by authors. However, they are not synonymous. Green chemistry focuses on the product/chemical/pharmaceutical itself, whereas sustainable generally includes all aspects of a product related to sustainability e.g. the shareholders, the stakeholders and the people applying and using the compounds when seeking for solutions that will work. (1st International Conference on Sustainable Pharmacy, Osnabrück 24/25 April 2008; http://www.dbu.de/550artikel27309_788.html).

of pharmaceuticals. Low toxicity against humans is already a prerequisite for registration of the most active pharmaceutical ingredients (APIs) and adjuvants. A sustainable extension of the concept of intrinsically safe pharmaceuticals results in the requirement that chemicals be quickly and fully degradable to harmless products when they enter the environment. This can be done by bacteria (biodegradation), light (photo degradation) or other non-biotic processes such as hydrolysis or oxidation. Li et al. (2008) reported thermal decomposition of penicillin G as treatment of the effluent of a production plant.

Synthesis and use of APIs and adjuvants should be effective, efficient and affordable. A sustainable molecule offers efficacy and efficiency of function combined with no or only minor unwanted side effects along its whole life cycle. According to the principles of sustainable chemistry, which also apply to sustainable pharmacy, the functionality of a molecule should not only include the properties necessary for its application, but also the ability to degrade completely upon entry into the environment, or, at least, to transform into harmless, inactive products. However, this is contrary to the common expectation that an API and an adjuvant should be stable to find its place in the market. The concept of "benign by design" holds big opportunities for companies and the environment However, more knowledge and further experience has to be collected on the full scope opportunities and limitations of this approach. This knowledge should be incorporated into the education of medicinal chemists and pharmacists. For the dissemination of this approach success stories are needed. Because the benign by design approach is a new concept one should be aware that a full and broad implementation in education, research and production will require some time i.e. a decade or more.

9.2.2 Stability of APIs

Conventional wisdom assumes that an API and adjuvant needs to be stable to be successful in the market. A closer look reveals that this is not necessarily the case. Some well-known APIs have been marketed very successfully for long time despite instability. Some ß-lactam antibiotics are stored as dry powder because of their sensitivity against hydrolysis until they are used. After reconstitution with water they can be stored in the fridge for a few days until use. Once excreted into waste water they are hydrolysed by non biotic and/or biotic processes. Some penicillins such as ampicillin are fully mineralized, while others such as piperacillin are at least deactivated (Längin et al. 2009). Other APIs are not stable under normal storage conditions but reach sufficient shelf life through storage in brown glass bottles to prevent photo decomposition. In ongoing research, we found that some APIs are well degraded in the standardized tests (e.g. according to EU or OECD) that are applied for biodegradability testing within new chemicals approval process (Table 9.1). Large amounts of the anti epileptic drug valproic acid have for example been used worldwide for more than 40 years (69 metric tons in Germany alone in 2006), despite its narrow therapeutical window. In standardized tests it is fully mineralized by environmental bacteria (Table 9.1).

Table 9.1 Biodegradability of selected pharmaceuticals from various classes in different OECD tests (Kümmerer and co-workers, unpublished, Kümmerer et al. 2000, Kümmerer 2007, Kümmerer and Al-Ahmad 1997). Criterion for ready biodegradability in 301 tests and inherent biodegradability in 302 tests is >60%

Active compound	OECD 301 D	OECD 301 F	OECD 302 B
Isosobiddinitrate	>90		
Mesalazin	>90	>90	
Acetylsalicylic acid		81	
Penicillin V	27		>90
Glufosfamide	53		72
Piracetam		>90	>90
Hydroxamic acid	50	90	
Valproic acid	72	78	
Cytarabin	40		>90

An analysis of data from our in-house biodegradability data base which comprises of 2,200 different chemicals of which some 500 have been tested in two or more tests (OECD test series 302 and 301), shows that currently 979 chemicals on the market are readily or inherently biodegradable (36% of all compounds), whereas the figure is 29% for pharmaceuticals from different chemical and therapeutical classes (28 out of 96). In these cases, only biodegradability under standardized conditions was investigated. These molecules were not the result of a targeted approach. Rather, sufficient biodegradability was achieved by chance.

However, these findings demonstrate that the good performance of a pharmaceutical within its application area is not necessarily a contradiction to good (bio)degradability after it has entered the environment. These findings also demonstrate that there is a hitherto as yet undiscovered and exploited potential for new and better biodegradable APIs. The data also demonstrate that (bio)degradability and efficacy are not necessarily mutually exclusive (see also below: ifosfamide vs. glufosfamide).

Correspondingly, sufficiently environmentally mobile and fully degradable chemicals offer the advantage that there is no need for advanced technical treatment. This allows for sustainable use of such pharmaceuticals in countries where there is only little or no effluent treatment. Environmental safety is included inherently. Therefore, molecular design of chemicals must include full functionality with optimized properties and reduced environmental impact at all life stages.

9.2.3 Stability vs. Reactivity

A new understanding would be to regard low biodegradability after use as an unwanted side effect and to include this aspect into pharmacovigilance (Kümmerer and Velo 2006). Another, more general look shows that the paradigm of the stability of APIs and adjuvants as an indispensable property for their application is questionable. Normally, we speak of the stability of a chemical without mentioning

the context of its "environment." We assume that the stability of a chemical is an intrinsic property of a chemical. However, this "stability" is the result of the interaction of a molecule with its environment. Stereochemistry and electronic properties of a molecule on the one hand, and the requirements set by its environment on the other, govern the interaction and the resultant lifetime. Therefore, the reactivity of a molecule depends on both the properties of the molecule and its environment. This is one of the basic principles of chemistry: change the conditions, e.g. temperature or moisture and a molecule may react in a different way or rate. It is this interaction that has to be in focus.

Access of light, pH-value and redox-potential vary along the life cycle of an API and an adjuvant (Fig. 9.1).

They differ for example during storage, in the human body and municipal sewage, sewage treatment or surface water. Bacterial diversity and bacterial density differ in these different environments. The metabolic diversity and the sheer number of bacteria and their potential and pathways for the breakdown of molecules (i.e. number and species of enzymes) differ. Other conditions of importance that differ are moisture light, temperature, oxygen concentration and pH.

Stability and degradability are a question of kinetics and thermodynamics, i.e. the relation between energies and the time scales of the different reaction pathways. Bioactive chemicals such as pharmaceuticals have to have a certain reactivity within their range of application. If they did not react they would not be bio-active

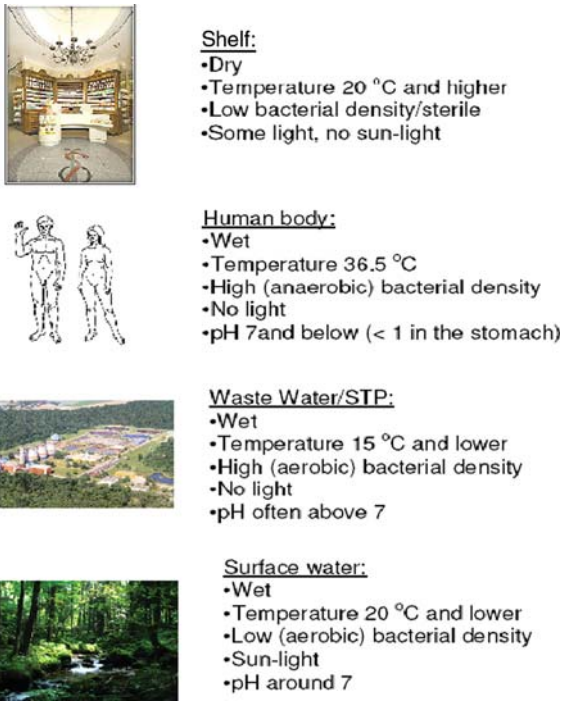


Fig. 9.1 Some selected physical, chemical and microbiological (reaction) conditions along the use and disposal

and therefore useless for their intended purpose. It should also be noted that some pharmaceuticals are applied as pro-drugs. Before they can exert their desired effects, pro-drugs are activated in the human body first.

All APIs would be useless without the reactivity necessary to produce effects in the body of the target organism. Any effect, wanted and unwanted, is based on some interaction of APIs with other molecules, e.g. receptors or enzymes. They display their reactivity within a special environment, e.g. within the human body, where they are activated in a specific manner. The knowledge described above will enable us to design APIs and adjuvants not only for optimised performance during their application but also within the latter stages of their life cycle. The challenge is to design a molecule in such a way that its lifetime is sufficient for its use but which is restricted to its intended environmental conditions. Critical life times can be derived from stability and physical-chemical properties, i.e. the temporal and spatial range of a chemical (Kümmerer 1996, Scheringer and Dunn 2002).

9.2.4 The General Approach

Designing APIs according to both the requirements of application and the environment, i.e. along their whole life cycle (Fig. 9.2), is quite ambitious. However, this goal is at the core of chemistry. Chemistry and the chemist's language address the relation of the structure of a chemical and its properties (e.g. its reactivity). Even small changes in the structure of a chemical may have tremendous effects on its properties. Benzene is (after metabolic activation) a carcinogen. It is only slowly biodegradable under aerobic conditions. Insertion simply of an oxygen atom into a carbon hydrogen bond results in a new compound with very different properties that are significant for its use and its fate in the environment – phenol. In contrast to benzene, phenol is readily aerobically biodegradable, is not carcinogenic and is active against bacteria. Therefore, it has long been used as a disinfectant. This fundamental connection between structure and properties can be used for the approach of benign by design (Daughton 2003, Kümmerer 2007, Boethling et al. 2007).

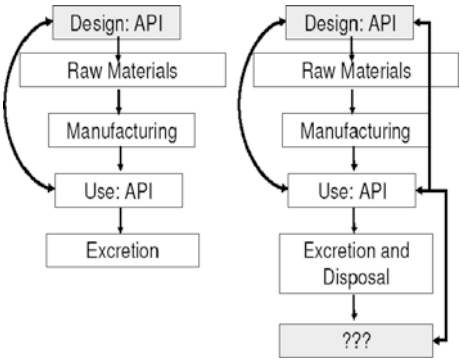
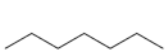
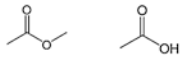
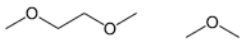
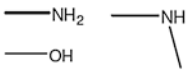
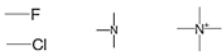
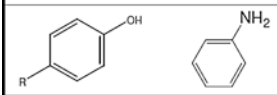
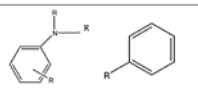


Fig. 9.2 Conventional (*left*) and sustainable approach for the design of new pharmaceuticals (*right*)

Table 9.2 Chemical functionalities and their impact on biodegradability

Preferable	Less preferable
	
	
	
	
	

The general approach is quite common for example for the development of pharmaceuticals with respect to reduction of unwanted side effects (Ekins 2007). The methodology applied to improve the medical performance of a new pharmaceutical entity can also be applied to include after use life aspects such as environmental properties. Targeted design and life cycle engineering of pharmaceuticals can also result in economical advantages in the long run, because fewer investigations may be necessary for the authorization of the new compound.

Chemical functionalities that have a positive impact on biodegradability are known (Table 9.2). This knowledge can be used to improve the biodegradability of pharmaceuticals if they are considered as part of molecules during the design/optimization phase. Within such an approach the active principles can and should be kept. Other parts of the molecule can be modified accordingly. Examples are ifosfamide and glufosfamide (Fig. 9.3).

Ifosfamide is not biodegradable, whereas glufosfamide is one of the best biodegradable anti-neoplastic compounds. The structural change not only results in improved biodegradability attributable to the sugar moiety, instead the whole molecule is much better biodegradable and deactivated in the environment. At the same time, any unwanted side effects are reduced compared to ifosfamide because of better uptake in the gut. It is well known for example that C-F-bonds, quaternary and tertiary C- and N-atoms and ether-oxygens reduce biodegradability (Table 9.2). In contrast, alcohols and esters are often well biodegradable. The length of an alkyl chain also has an impact on biodegradability. These rules and experiences need to be refined and broadened. Codified rules and expanded profiles allow the theoretical design of molecules and the assessment of their properties before they are even synthesized. However, human expertise is limited. Molecules that contain different

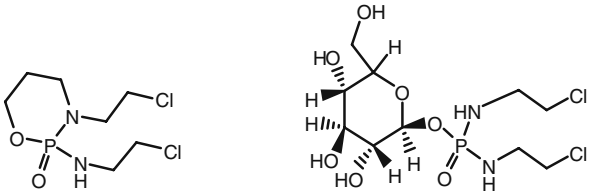


Fig. 9.3 Ifosfamide (*left*) and ß-D-Glc-IPM (INN: Glufosfamid; *right*)

chemical functionalities such as pharmaceuticals may not be assessed properly by the experience of the expert on the basis of simple rules like the ones presented in Table 9.2.

The full functionality of a molecule includes the properties necessary for good performance within all its life stages– not only during application.

Modern computer software enable screening of such molecules, not only for properties that are of interest for medical reasons, but also for environmental properties such as (bio) degradability. They also allow for a benign by design approach. Within the last decades, expert computer-based systems have been developed that assist humans with the handling and application of this complex type of knowledge (Boethling and Mackay 2000). This approach is currently widely in use within the pharmaceutical industry and to some extent also in the chemical industry for optimization of application-related properties such as efficacy or stability. Starting from a lead structure, the desirable properties of a molecule are improved by systematic variation of its chemical structure. At the same time, unwanted properties such as mutagenicity or toxicity can be reduced. As few side effects as possible means that the inherent safety of the chemical has been improved and that the total functionality of the molecule has also been improved.

In ongoing research we have been able to improve the activity of a lead structure suitable for anti cancer treatment. At the same time, its biodegradability could be improved by continuously monitoring the biodegradability of new structures by application of quantitative structure activity relation ships (QSARs).

One advantage of such approaches is that it is not necessary to synthesise all the molecules that may be of interest. In contrary a structural formula is enough for such screening purposes. This allows for a very early and comparatively cheap evaluation of the environmental properties of candidates.

The examples described above demonstrate the feasibility of this approach. If the different conditions and dependencies along the life cycle of a molecule are taken into account, stability during the application phase and degradability thereafter are not necessarily in opposition.

References

Anastas PT, Warner JC (1998) Green Chemistry: Theory and Practice. Oxford University Press, Oxford, New York

Boethling RS, Mackay D (2000) Handbook of Property Estimation Methods for Chemicals – Environmental and Health Sciences. Lewis Publisher, Boca Raton

Boethling RS, Sommer E, DiFiore D (2007) Designing small molecules for biodegradability. Chem Rev 107, 2207

Cairns J, Jr, Mount DI (1990) Aquatic toxicology. Part 2. Environ Sci Technol 24, 154–161

Calza P, Medana C, Carbone F, Giancotti V, Baiocchi C (2008) Characterization of intermediate compounds formed upon photoinduced degradation of quinolones by high-performance liquid chromatography/high-resolution multiple-stage mass spectrometry. Rapid Commun Mass Sp 22, 1533–1552

Clark JH (2006) Green chemistry: today (and tomorrow). Green Chem 8, 17–21

Clark JH, Smith P (2005) Basic principles of green chemistry. Innov Pharma Technol 16, 94–97

Daughton CG (2003) Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ Health Persp 111, 757–774

Dohmann M (2004) Maßnahmen zur Verringerung der Gewässerbelastung durch Arzneimittelrückstände und Umweltchemikalien. Gewässserschutz, Wasser, Abwasser 193, 25/7

Drewes JE, Heberer T, Reddersen K (2002) Fate of pharmaceuticals during indirect potable use. Water Sci Technol 46, 73–80

EU (2003) EU 2003 Directive 2003/87/EC of the European Parliament and of the Council of 13 October 2003 establishing a scheme for greenhouse gas emission allowance trading within the Community and amending Council Directive 96/61/EC, L 275/32 EN Official Journal of the European Union 25.10.2003

Ekins S (ed.) (2007) Computational Toxicology. John Wiley and Sons, Hoboken

El-Khateeb M, Appleton TG, Charles BG, Gahan LR (1999) Development of HPLC conditions for valid determination of hydrolysis products of cisplatin. J Pharm Sci 88, 319–326

Götz K, Keil F (2007) Medikamentenentsorgung in privaten Haushalten: Ein Faktor bei der Gewässerbelastung mit Arzneimittelwirkstoffen? 9 UWSF 19, 180–88

Heberer T, Feldmann D (2005) Contribution of effluents from hospitals and private households to the total loads of diclofenac and carbamazepine in municipal sewage effluents – modeling versus measurements. J Hazard Mater 122, 211–218

Isidori M, Lavorgna M, Nardelli A, Parrella A, Previtera L, Rubino M (2005) Ecotoxicity of naproxen and its phototransformation products. Sci Total Environ 348, 93–101

Isidori M, Nardelli A, Pascarella M, Rubino M, Pascarella A (2007) Toxic and genotoxic impact of fibrates and their protoproducts on non-target organisms. Envrion Int 33, 635–641

Jones OHA, Green PG, Voulvoulis N, Lester JN (2007) Questioning the excessive use of advanced treatment to remove organic micro-pollutants from waste water. Environ Sci Technol 41, 5085–5089

Kümmerer K (1996) The ecological impact of time. Time Soc 5(219–235), 1996

Kümmerer 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 Chem 9, 899–907

Kümmerer K (2008) Strategies for the Reduction the Input of Pharmaceuticals into the Environment. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risk. 3rd edition, Springer Publisher, Berlin Heidelberg New York, 433–440

Kümmerer K (2010) Design of Inherently Safe Molecules. In: Nelson W (ed.) Oxford Handbook of Green Chemistry: From Molecular Design to Process Scale Up. Oxford University Press, Oxford, New York, in press

Kümmerer K, Al-Ahmad A (1997) Biodegradability of the anti-tumor agents 5-fluorouracil, cytarabine and gemcitabine: impact of the chemical structure and synergistic toxicity with hospital effluents. Acta Hydroch Hydrob 25, 166–172

Kümmerer K, Al-Ahmad A, Bertram B, Wießler M (2000) Biodegradability of antineoplastic compounds in screening tests: improvement by glucosidation and influence of stereo-chemistry. Chemosphere 40, 767–773

Kümmerer K, Velo G (2006) A new topic of importance in pharmacovigilance. Drug Safety 29, 371–373

Längin A, Alexy R, König A, Kümmerer K (2009) Deactivation and transformation products in biodegradability testing of ß-lactams amoxicillin and piperacillin. Chemosphere 75, 347–354
Lee C, Lee Y, Schmidt C, Yoon J, von Gunten U (2007) Oxidation of N-nitrosodimethylamine (NDMA) with ozone and chlorine dioxide: kinetics and effect on NDMA formation potential. Environ Sci Technol 41, 2056–2063
Li K, Yediler A, Yang M, Schulte-Hostede S, Wong MH (2008) Ozonation of oxytetracycline and toxicological assessment of its oxidation by-products. Chemosphere 72, 473–478
Matamoros V, Bayona JM (2006) Elimination of pharmaceuticals and personal care products in subsurface flow constructed wetlands. Environ Sci Technol 40, 5811–5816
Méndez-Arriaga F, Esplugas S, Giménez J (2008) Photocatalytic degradation of non-steroidal anti-inflammatory drugs with TiO_2 and simulated solar irradiation. Water Res 42, 585–594
Metzger S, Kapp H, Seitz W, Weber WH, Hiller G, Süßmuth W (2005) Entfernung von iodierten Röntgenkontrastmitteln bei der kommunalen Abwasserbehandlung durch den Einsatz von Pulveraktivkohle. GWF Wasser Abwasser 9, 638–645
Naddeo V, MeriçS, Kassinos D, Belgiorno V, Guida M (2009) Fate of pharmaceuticals in contaminated urban wastewater effluent under ultrasonic irradiation. Water Res 2009 May 28. [Epub ahead of print]
Nowotny N, Epp B, von Sonntag C, Fahlenkamp H (2007) Quantification and modeling of the elimination behavior of ecologically problematic wastewater micropollutants by adsorption on powdered and granulated activated carbon. Environ Sci Technol 41, 2050–2055
Qiting J, Xiheng Z (1988) Combination process of anaerobic digestion and ozonization technology for treating wastewater from antibiotics production. Water Treat 3, 285–291
Ravina M, Campanella L, Kiwi J (2002) Accelerated mineralization of the drug diclofenac via Fenton reactions in a concentric photo-reactor. Water Res 36, 3553–3560
Rizzo L, Meric S, Guida M, Kassinos D, Belgiorno V (2009) Heterogenous photocatalytic degradation kinetics and detoxification of an urban wastewater treatment plant effluent contaminated with pharmaceuticals. Water Res. 2009 June 27. [Epub ahead of print]
Scheringer M, Dunn MJ (2002) Persistence and Spatial Range of Environmental Chemicals. Wiley VCH, Weinheim
Schröder HF (2002) Mass spectrometric monitoring of the degradation and elimination efficiency for hardly eliminable and hardly biodegradable polar compounds by membrane bioreactors. Water Sci Technol 46, 57–64
Schulte-Oehlmann U, Oehlmann J, Püttman W (2007) Arzneimittelwirkstoffe in der Umwelt – Einträge, Vorkommen und der Versuch einer Bestandsaufnahme. UWSF 19, 168–179
Strässle R (2007) Mikroverunreinigung: Ozon als Lösung? Umwelt Perspektiven 8, 34–37
Ternes TA, Joss A (eds.) (2006) Human Pharmaceuticals, Hormones and Fragrances – The Challenge of Micropollutants in Urban Water Management. IWA Publishing, London
Vasconcelos TG, Henriques DM, König A, Martins AF, Kümmerer K (2009b) Photo-degradation of the antimicrobial ciprofloxacin at high pH: identification and biodegradability assessment of the primary by-products. Chemosphere 76, 487–493
Vasconcelos TG, Kümmerer K, Henriques DM, Martins AF (2009a) Ciprofloxacin in hospital effluent: degradation by ozone and photoprocesses. J Hazard Mater 169, 1154–1158
Watkinson AJ, Murby EJ, Costanzo SD (2007) Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling. Water Res 41, 4164–4176
Wei-Hsiang C, Young TM (2008) NDMA formation during chlorination and chloramination of aqueous diuron solutions. Environ Sci Technol 42, 1072–1077
Wenzel H, Larsen HF, Clauson-Kaas J, Høibye L, Jacobsen BN (2008) Weighing environmental advantages and disadvantages of advanced wastewater treatment of micro-pollutants using environmental life cycle assessment. Water Sci Technol 57, 27–32

Part III
Use and Disposal of Pharmaceuticals

Chapter 10
Options for a More Environmentally Friendly Handling of Pharmaceuticals

Konrad Götz and Jutta Deffner

10.1 Background

Findings from a large number of studies on pharmaceutical residues in the water cycle, particularly drinking water, are now available (for an overview see Schulte-Oehlmann et al. 2007, Sumpter, Chap. 2, this book). The paths by which they enter the environment are also known. In the course of normal use, medications are taken by patients, metabolised within the body and subsequently excreted, largely in urine. Human pharmaceuticals can also end up in the water cycle as a result of inappropriate household disposal via the washbasin or toilet.

In the meantime, several signs bear witness to the long-term effects of these substances on the environment (e.g. in the aquatic domain: Jobling et al. 1996, Schulte-Oehlmann et al. 2004). There are, however, no substantiated results on how the consumption of drinking water with ultra-trace levels of contamination affects humans. Nor are there any strategic considerations thus far as to whether and how this incalculable risk should be tackled in future (Dürr and Hollert 2007) and which precautionary environmental measures would be capable of reducing or preventing the entry of active pharmaceutical substances into the water cycle.

10.2 Objectives of Strategic Considerations

This chapter is thus devoted to the options available for reducing such entry by changing common practices in the prescription, sale and use of drugs and the disposal thereof within the German context. It cannot be denied that pharmaceuticals are indispensable when it comes to guaranteeing the best possible health for the population. They are deployed for the single purpose of curing disease or relieving symptoms, and strategies intended to reduce entry into the environment must never lose sight of this paramount objective. Nevertheless, the vital question here concerns

K. Götz (✉)
Institute for Social-Ecological Research, Frankfurt/Main, Germany
e-mail: goetz@isoe.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_10,

the potential for such strategies in areas where the health care system, environmental policy and social discourse overlap. In contrast to the technical options for filtering out pharmaceutical residues that have already entered the water system (Püttmann et al. 2008) or the future development of more biodegradable active pharmaceutical substances (Kümmerer and Schramm 2008), here we are concerned with changing the way in which medications are handled on an everyday basis.[1]

In looking for ways to improve environmental awareness in connection with the handling of pharmaceuticals, the first step is to find possible starting points from which to bring about a reduction of contamination. With medicines being part of our daily consumer behaviour, there are varied and complex forms of interaction between the patients who consume the drugs, the doctors who prescribe them, the pharmacists who advise and sell them, the pharmaceutical industry, and the health care system, as well as a whole series of different interests and expectations. We have attempted to depict these relationships in Fig. 10.1.

We identify different factors that influence the quantities and handling of drugs:

- The prescribing practice of doctors
- Doctor-patient relationship, expectations when visiting the doctor
- Purchase behaviour and usage amongst patients/consumers
- Sales interests on the part of players within the health care system (doctors, pharmacists, pharmaceutical industry)
- Waste disposal patterns: risk of inappropriate disposal

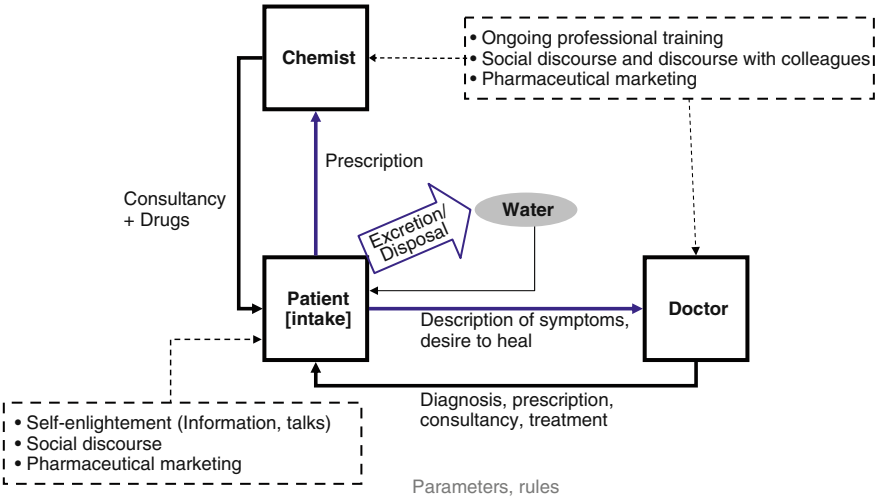


Fig. 10.1 System and relationships focusing prescription, selling and use of drugs

[1] All three strategic approaches have been addressed in the project *start* – strategies for dealing with active pharmaceutical substances in drinking water". The project was funded by the German Federal Ministry of Education and Research (www.start-project.de).

The essence, therefore, is all about the behaviour of players involved in this interactive structure – which is why the bundle of measures in question is referred to as the behaviour-related strategy. In the following we describe the methodological approach by which we gained data to underpin the development of the strategy.

10.3 Approach

The fundamentals for selecting and fleshing out measures to bring about change in current prescribing, usage and disposal patterns were developed in several stages. Interdisciplinary research of the literature and methods formed the basis from which to determine the current status of research and empirical methods for the topics at stake.

This was followed by several empirical surveys:

- Face-to-face interviews with doctors (qualitative; with topic guide)
- Focus groups with pharmacists to explore the topic and establish their perception of risk
- Standardised survey on the disposal of drugs (nationwide, representative of the population)

The first two stages (qualitative interviews, focus groups) served to explore the two groups of players for their awareness and knowledge of pharmaceutical residues in water. The aim was to pinpoint reaction patterns and sound out the extent to which people regard the topic as a problem, along with any arguments underlying possible dismissive or sympathetic reactions. Another interesting aspect was to examine how the topic is viewed regarding its impact on the relationship between doctor or pharmacist and patients, and how people rate any available opportunities via which to change their personal actions. Qualitative methods were picked as the best way to deal with these questions, which meant using focussed interviews based on a topic guide to interview the doctors. Qualitative research in general aims to gather an in-depth understanding of human behaviour and the reasons that govern such behaviour. Qualitative methods investigate the why and how of decision making.

A total of 16 doctors from the Rhine-/Main-/Neckar-region were interviewed in sessions lasting approximately 60 min. These health professionals worked either as general practitioners or in hospitals. Their specialities ranged from general/internal medicine through environmental medicine/allergology, endocrinology, oncology, gynaecology down to psychiatric medicine. A total of 20 respondents took part in the pharmacist focus groups. Two thirds of these participants held senior posts at registered urban and rural pharmacies, while the remaining third worked as chief clinical pharmacists in Greater Frankfurt. The inquiries were conducted during the second half of 2006. The data was subjected to content analysis and

the results subsequently discussed within the transdisciplinary framework of the project.[2]

In addition, a representative survey of the German population was conducted to investigate how consumers dispose of unused drugs (Götz and Keil 2007).

Based on the empirical findings, an initial set of behaviour-related measures was developed. From the array of per se meaningful or abstractly feasible measures generated in this way, a strategic selection was made according to pragmatic criteria such as implementability within society, financeability and the likelihood of seeing results within a foreseeable time frame. The resultant strategic approach was discussed amongst experts (as part of the project) and with professionals (from the environmental, pharmaceutical, health, water and waste water treatment sectors) at the transdisciplinary stakeholder workshops This was followed by a phase of adjusting, fine tuning and evaluating the measures, which in turn led to paring down and modification. The result of this process is outlined below, and represents those measures that manifested stability throughout.

10.4 Results – Strategic Approach of Behaviour Modification

The proposed initiatives for a behaviour-related strategy can be divided into three categories:

- Political measures to alter general conditions (environmental objectives, classification of pharmaceuticals)
- Communication measures (to create an awareness of the problem amongst professional players)
- Measures to support and facilitate changes in behaviour

Whereas the communicative measures and change in the general conditions will both take effect with a certain time delay, the measures related to behaviour are in a position to make an immediate impact on reducing the entry of substances into the water system. Designed to initiate, motivate and support behavioural change, these measures aim on the one hand to reduce the amount of pharmaceuticals being prescribed and consumed, and on the other to ensure a means of disposing of unused drugs that does not contaminate the aquatic system. Table 10.1 provides an overview of the measures.

[2] For the methodology of interviews based on topic guides and content analysis see, for example, Lamnek (2005).

Table 10.1 Overview of measures for a behaviour-modification strategy

Field of action	Measure
Overarching parameters	– General framework constituting an environmental objective that defines the protection of the ground and surface water from the entry of medications – Environmental classification list for the major drugs
Bringing about change in problem awareness (doctors/pharmacists)	– Initiating a discourse on the issue amongst doctors – Enshrining the problem in the continuing professional training of doctors and pharmacists
Avoiding and reducing the use of drugs	– Controlling drugs demand through transparency of costs and quantities, along with co-payments – Prescribing of options that do not involve drugs
Disposing of drugs	– Uniform standards for disposal, along with the development of a basic system for pharmacies to take back unused drugs – Behaviour-related campaign to provide information on appropriate disposal – Clear disposal instructions on drugs packaging

10.4.1 Creating Parameters and Environmental Classification for Pharmaceuticals

Research of existing approaches designed to reduce the entry of medications into the water system has shown that action-changing measures can only take effect once overarching, legally defined environmental goals geared to stopping medications from entering ground and surface water are in place. Sweden demonstrates (see Wennmalm and Gunnarsson, Chap. 16, this book) how it is only with resolute rulings of this kind that politicians, the general public and players within the health care system actually recognise and agree on the need for such an objective: Stockholm County Council lobbies primarily for solutions to those environmental problems arising from activities by provincial government, for example in its capacity as the body in charge of the public health care system. Reducing contamination to water, air and soil from pharmaceutical residues is one of the most readily acknowledged goals (Wennmalm 2003a, b).[3]

All measures arising from this, such as the environmental classification of pharmaceuticals (Wennmalm and Gunnarsson 2005), the list of recommended pharmaceuticals as guidance for doctors (illustrative material: Stockholms Läns landsting 2006a[4]), monitoring of sewage and drinking water contamination from

[3] Another important objective is to reduce air pollutant emissions from the transport sector and thermal power plants.

[4] Stockholm Län Landsting can be translated as Stockholm County.

pharmaceutical residues (Stockholms Läns Landsting 2006b) along with various offers of information for doctors and the general public, stem from a voluntary commitment on the part of the province or county. In other words, all activities on the part of the province that are geared to a third party are voluntary.

In Germany, any *change to the parameters in this context* could be initiated by the Federal Environment Agency, and anchored in environmental law in the middle to long term (5−10 years). A committee of experts would need to decide on (the need for) corresponding guidelines, procedural directives or enactments, to lay down critical values or reduction goals for the entry of pharmaceuticals into the environment.

Another aspect of the measure is to change the laws and directives governing pharmaceuticals and the disposal thereof in such a way as to rule out or reduce the contamination of aquatic systems by pharmaceutically active substances and/or to create awareness that such substances represent potential contaminants. Overall, such changes to the overarching parameters are intended as a precautionary measure, using environmental activities to tackle the risk to the water cycle posed by pharmaceutical residues, a problem which is, admittedly, difficult to define in objective terms.

To this end, it would be expedient to launch an ongoing *environmental classification of pharmaceuticals (list of recommendations)*, in which criteria constituting a risk to the environment, along with the environmental hazard posed by medicinal active substances, are assessed within a clear classification schema. The evaluation model should be relatable to existing criteria for environmental risk assessment (e.g. according to EMEA 2006) and also give particular consideration to the fact that the active substances are water borne and relevant to water treatment works. Substances to be classified are selected not merely on the basis of the potential danger they pose, but also on the amounts of daily doses sold (here: for Germany). It is recommended that the concept should borrow from the classification system developed in Sweden (Apotheket 2006, Wennmalm and Gunnarsson 2005). If such a list recommending selected drugs is to meet with the acceptance of doctors, pharmacists and also pharmaceutical manufacturers, it needs to be compiled by an independent body.

There are several other demands that the list of recommendations needs to fulfil. For instance, it should be user friendly implemented in practitioners' offices and/or be available for interested patients in order to facilitate a correct application. This means that the underlying intention of the environmental assessment must be immediately obvious to the user. Nor should the impression be created that consideration of the environmental aspects is at odds with the doctor's imperative to heal. Appropriate information material and consultancy offers must be developed in order to launch the measure. Attempts should also be made to integrate the environmental classification list into relevant works of reference and recommendation, and include it in information systems (e.g. German "Rote Liste®" − red list; an advisory compendium for doctors to choose medicines − software for choosing medicines).

10.4.2 Bringing About Change to Problem Awareness Amongst Doctors and Pharmacists

The qualitative interviews revealed a somewhat low awareness of the problem amongst most of the doctors, despite their appreciating the logic of the entry route after brief discussion of the issue. The study, which is not representative in a statistical way but shows typical patterns of reactions, revealed typical lines of argument and patterns of interpretation from which a possible procedure might be inferred: the doctors themselves miss substantiated knowledge (facts, research results) about individual residues of active substances in aquatic systems and the subsequent consequences of this. Antibiotics and sex hormones are the things they normally tend to associate with the problem. It was also established that some doctors have a relatively vague grasp of how active substances decompose. In order to effect a change in problem awareness, doctors must be given the chance to form an opinion as medical professionals, on the basis of discourse and not within a given framework. During the empirical study, doctors were seen to have different reservations to intervention: they are afraid that other goals besides healing could take centre stage, or else they seem "over-sensitive" to new directives as a result of the "ongoing health reform" in Germany. This is why changes to professional behaviour, e.g. the willingness to change prescribing practices, must be come about at the doctors' own volition.

By virtue of their professional responsibility, pharmacists consider themselves to be more involved in the problem under review here than the doctors; they refer to figures on pharmaceutical waste and their own experience of mere fractions of such waste being returned to their pharmacies. As a result of their training and daily work, they are familiar with the material aspects of medicines, and immediately appreciate the link between the intake of medicines and the occurrence of active substances in the water cycle. They recognise and subscribe to the need for prevention and forward-looking action, but see their own capability in this respect essentially limited to consultancy and offers of proper disposal. Consultancy can exert a substantial influence on the increasingly significant use of over-the-counter products (e.g. countless Hanalgetics).

This implies the need to take the pharmaceutical sector on board in initiating a discussion on the incalculable risk and a possible precautionary strategy. To this end, targeted publications can be placed in print and online media, in forums and platforms acknowledged and deemed plausible by pharmacists (e.g. specialist medical media, platforms of professional associations), and in papers delivered at congresses, conferences and seminars for specialist journalists. Such action could bring about a change in professionals' awareness of the problem in the medium term.

Discursive offers of this kind must be directed at different target groups within the professional groups, targeting precisely those areas where empirical research has revealed differing reactions to the topic. These range from spontaneous rejection stemming from a sense of non-responsibility for the environmental problem down to a great show of openness and interest in the issue. The latter reaction may be linked

to a real need for information and an appreciation of the wisdom of preventative measures that admits one's own partial responsibility; this, in turn, can act as a trigger for action.

To support the opinion-forming process, problem awareness and action-related insights can form part of the mandatory continuing professional training for doctors and pharmacists (Bundesministerium für Gesundheit 2007, German Ministry for Health). Such training seeks to explain and discuss appropriate conduct for everyday professional life. Here, the residue issue should be embedded in "healing" topics dealing with drug prescription or consultancy practice as well as in those dealing with cost reduction.

10.4.3 Avoidance and Reduction of Pharmaceutical Consumption

Of critical significance to the entry of pharmaceutical residues into the water cycle are human excretions, predominantly urine. Suitable measures for preventing entry therefore tackle the problem from two different perspectives: either via a reduction in the amount of medications prescribed, or via the choice of active substance or alternative therapies that help to avoid the deployment of environmentally hazardous substances. Measures of this kind call for a willingness on the part of doctors to change their prescribing practice. This also presumes patient acceptance of a changed approach to medication. The measures discussed in what follows are to be seen in connection with the more economic or more efficient organisation of the health care system – synergy effects are desirable, and without them such measures could not be justified.

10.4.3.1 Controlling the Demand for Pharmaceuticals Through Transparent Costs and Quantities and via Co-payment

The fact that cost transparency is largely absent when it comes to medications (and other medical measures) for individuals with (public) health insurance in a state-run welfare system contributes to the phenomenon of the so-called moral hazard (Pauly 1968).[5] In the pharmaceutical context this means that patients accumulate drugs without using them, whether due to non-use or double prescriptions. Some of these medications are then disposed of (Götz and Keil 2007, Bronder and Klimpel 2001, Schröder 2005), thus creating the risk of improper disposal and entry into the water system.

[5] The Moral Hazard thesis assumes that health insurance companies and state health care systems induce people to make a greater claim on medical services than is actually necessary. The reason for this is that each insured person is keen to enjoy as many benefits as possible, since contributions are levied regardless of individual claims. In addition, the insured person is afraid of getting a raw deal if they only demand a minimal degree of medical attention and thus find themselves financing the "entitlement mentality" of others. Such behaviour is not immoral, but economic (Bertelsmann-Stiftung 2006).

Voluntary measures (such as the so-called LKI,[6] which is information on service and costs, or patient receipts) which are intended to create better cost awareness have not been particularly well received by patients thus far (Zentralinstitut 2003). However, synergy effects that promote better cost awareness could come about with the introduction of the imminent electronic health card. Medications which have been prescribed and actually bought are saved, and both the doctor and the pharmacist can see which active substances were prescribed. This means than in the event of an increased number of prescriptions for the same or similar active substances, the doctor or pharmacist can ask the patient how they handle the prescriptions or drugs. Such feedback might well encourage a change in behaviour or lead to a change in the nature of a prescription or the amount prescribed, or indeed to modified therapy. The measure would call for agreement between the medical associations and the insurers, and for changes to the organisation of doctors' surgeries.

The option of a higher co-payment is often discussed as the measure most likely to increase cost efficiency and transparency in the health care system (Bertelsmann-Stiftung 2006, Gruber 2006). As far as the accumulation of medications in private households is concerned, it is fair to assume a synergy effect. However, such models must take into account special hardship regulations for the chronically ill and socially disadvantaged patients.

10.4.3.2 Prescribing Options that Don't Involve Drugs

In addition to drugs and drug therapy, this initiative should enable doctors to "prescribe" options that promote health in general as part of an overall regime that effectively prevents illness and thus reduces the consumption of drugs. However, such prescriptions must comply in Germany with the so-called "pre-printed form agreement", i.e. a corresponding form has to be created and duly accepted by the health insurance schemes. Prescriptions of this kind that encourage a healthy lifestyle are, for example, action sports, walking, back training or changing one's diet. Experiences from Sweden prove that patients accept such prescriptions and that issuing a "prescription" is more binding than if the doctor merely recommends a change in behaviour during the doctor-patient consultation. Moreover, this can also go some way towards satisfying patients' expectations of their doctor (the desire for a prescription). There are already some pilot schemes in Germany that seek to implement these initiatives; one example would be the campaign sponsored by the *Landesärztekammer Hessen* (Doctors' Association for the State of Hesse) entitled "Get Fit and Healthy with the Exercise 'Prescription'" (Zentralinstitut 2003). Health insurance companies promote other initiatives such as bonus schemes that are geared towards prevention; they allow discounts if people avail themselves of certain health-promoting offers. It would be possible to implement an initiative of this sort in the short term (horizon: 2–3 years).

---

[6] LKI is the German abbreviation for benefit and cost information.

10.4.4 Disposal of Medicines

The representative survey that examined people's behaviour in relation to the disposal of medicines revealed that the practice of disposing of leftover medicines into the sewage system is far more widespread that anticipated. For example, 10.2% of respondents "always" dispose of liquid medicine residues via the toilet or washbasin; a further 8.3% "often" do this, 13.1% "sometimes" do so and 11.8% "rarely". This means that 43.4% of the population practise this form of incorrect disposal with varying degrees of frequency (Götz and Keil 2007). It is fair to assume that these high scores can, amongst other things, be traced back to the current (contradictory) information policy. The various advice dispensed on how to dispose of medicines includes returning them to pharmacies (Technikerkrankenkasse 2006), consigning them to "problematic waste" collections (Bayerisches Landesamt für Umwelt 2006), "hiding" them in non-recyclable waste (e.g. www.der-gruene-faden.de) and flushing them down the toilet (e.g.www.selbstbehandlung.de). The expert interviews confirmed these contradictions: doctors as well as pharmacists had widely differing views as to how old or unused medicines should correctly be disposed of. This allows us to conclude that the corresponding information for patients who quiz their doctor or pharmacist is similarly contradictory. Conjecture about how leftover medicines are subsequently handled is even more vague and contradictory. Although people on drug therapy are able to get information about correct disposal (for example, on local authorities' websites or in brochures produced by waste disposal companies), there is nonetheless no proactive and above all uniform communication about how to deal with this properly. It is doubtless true that the disposal of medicines is a "topic of low interest" because people presume that it has been sensibly regulated, and no institution feels truly responsible for it. This is aggravated by the fact that the separation of waste impacts upon the disposal of medicines insofar as liquid medicines are poured down the sink so that, for example, empty glass bottles can be recycled.

Given this background, the objective should still be to create a national (and if possible, EU-wide) consensus that medicines from private households should be disposed of exclusively via pharmacies or sites where problematic waste is collected.[7] One prerequisite is that pharmacies should continue to accept drugs voluntarily for disposal, free of charge.

This measure has to be cost-neutral for pharmacies, and one would need to make it easier to integrate the relevant logistics into their daily work routine. Pharmacists should not be obliged to separate waste; priority should be given to protecting water supplies.

The qualitative interviews demonstrate a fundamental willingness on the part of pharmacists to continue with the task of drug disposal in the future. They see the offer to collect unused drugs as a valuable customer service, and its association with

[7]In June 2009 the main German reverse logistic cancelled their services due to changes in the German legislation on packaging. This makes the need for a clear and easy to understand return system for unused drugs even more urgent.

protecting drinking water fits their professional image and how they see themselves. In future, drug manufacturers and the disposal logisticians (Vfw-Aktiengesellschaft 2002) they employ have to commit themselves by corresponding communication and/or waste legislation to integrate the goal of water protection in their systems and processes of product and waste circulation.

This should be backed up by a wide-ranging, professionally planned and designed campaign to educate the population about the appropriate disposal of unused medicines. Positive arguments should be used first to motivate people to handle them correctly, but consumers should also be warned about incorrect disposal in the sewage system. A wide variety of communication routes are necessary for a campaign of this sort; it must be subtly matched to different target groups and their media.

In addition, self-regulation or a Europe-wide statute should oblige drug manufacturers to print information about the correct disposal of medicines on both their packaging and instructions.

Offering drugs in variable pack sizes can likewise help to minimise unnecessary residues. Although doctors state that this problem has improved in recent years as a result of the health service reform, it has still not been comprehensively resolved. Particularly when it comes to chronic illnesses (e.g. Alzheimer's, Aids, cancer or psychological conditions) there is a lack of small or very small starter packs which can be prescribed to test tolerance. For reasons of hygiene, doctors do not think it advisable to provide drugs in single portions, without packaging (as for example happens in the USA); pharmacists share their view because they don't believe this would be cost-effective. However, it could make sense (for hospitals in particular) to identify each tablet individually on the blister with its name, batch number, expiry date and a code, thereby quickly and simply stating the necessary information so that single portions can be passed on or given by doctors to needy patients (an altogether common practice that is nonetheless not allowed today, as emerged from interviews with doctors).

10.5 Discussion and Consequences

One must initially examine why some initiatives were rejected during the course of the process. There is also the question of the extent to which the proposed initiatives are suitable in terms of their efficacy and costs when it comes to combating the hitherto uncertain effects of drug residues in water; this also entails open questions about the strategy development process.

Initiatives to create an awareness of the problem among doctors and pharmacists do not explicitly deal with training and education, since the curricula at higher education institutes are in any case being systematically updated, and the environmental relevance of medicines is gradually being taken up. One can assume that pharmacists and health professionals who will increasingly be informed about this topic via debate and ongoing training will also, for example, take it up and/or implement it in their courses.

Early on in the process of coming up with initiatives there was also some discussion within the overall context of the project about decreasing the amounts prescribed by changing the ways in which they are administered. Consideration was given to the fact that certain methods (enteral, parenteral, transdermal) can lead to different levels of excretion via urine, and that by replacing oral ingestion with other methods one can use these effects to achieve lower excretion rates. However, these effects differ greatly depending on the active substance, and the use of transdermal systems can even lead to disadvantages for the patient (incorrect dosages, allergies to plasters, higher costs). This requires research in order to eradicate such obstacles and develop new drugs and/or ways of administering them.

The majority of initiatives that incorporate the behaviour-related strategy (environmental objectives, classification and awareness of the problem) manifest an indirect and thus non-quantifiable efficacy in relation to the desired reduction. Nevertheless, they are important in terms of an overall strategy because they form the basis for the introduction and subsequent effectiveness of other initiatives.

When it comes to the effectiveness of communication initiatives that create an awareness of the problem among doctors and pharmacists, one has to bear in mind that they do not immediately and directly reduce the entry of active drug ingredients into the water cycle. However, the empirical studies that have been conducted have shown that they are a prerequisite if doctors and pharmacists are to devote themselves to the problem and take appropriate action.

At this stage it is also impossible to assess reliably the effectiveness of those initiatives that are linked to environmental classification and the use of a recommended list of more eco-friendly drugs because it is hard to put a figure on the degree of implementation and use within the pharmaceutical environment. The experiences from Sweden nonetheless demonstrate that, within the space of four and a half years, 77% of doctors consult the recommended list when selecting drugs.[8] It is difficult to estimate the extent to which this figure can be applied to the situation in Germany or even Europe, because the Swedish market is smaller and more state ruled than in other countries. Nevertheless, it shows how a targeted information campaign for professionals can reach its users.

It is equally difficult to use the available data to estimate (for example, at the level of the DDD[9]) how many drugs can be categorised as unnecessary without impacting negatively on patient care – thereby allowing them to be prescribed and/or sold less (initiatives to improve transparency about cost and quantities, plus those relating to non-drug prescriptions).

When it comes to estimating the effectiveness of disposal initiatives one is faced with the problem that there is a virtual lack of reliable figures as to the amount of drugs (tonnes or DDD) that, for example, accumulate in households every year (as a result of non-compliance, stocking up, etc.) and are then disposed of. This is

[8] From correspondence with Siv Martini, Stockholm County Council, Department of Drug Management and Informatics in May/June 2007.

[9] DDD: Defined Daily Dose.

aggravated by the fact that it is almost impossible to estimate the quantity of drugs that are disposed of via the toilet or washbasin. As already mentioned, we have data relating to the frequency of disposal, but not the amounts involved. Moreover, one would need to pay attention to the ratio of liquid to solid medicines, since liquids are far more often disposed of via the water cycle (Götz and Keil 2007). Cautious estimates of the percentage of old medicines disposed of every year in Germany range from 10 to 20% of drugs prescribed (statutory health insurance schemes) (Ärzte-Zeitung 2002). This would correspond to just less than 4 billion DDD per annum[10] or 5,700 t/annum (figures derived from BLAC 2003). Despite a lack of clarity about the precise amounts, the data gathered as part of the "Start" project allows one to estimate that approximately 14% of these old medicines are disposed of via toilets and washbasins (which would correspond to approx. 770 t/annum for Germany, basis 2003). This kind of figure could be considerably reduced in the medium term via the above-mentioned initiatives. This example demonstrates how difficult it is to make a precise estimate of the impact, one which would need to be based on exact figures instead of estimates that rely on specific assumptions. Neither does it take account of the fact that different groups of active substances present different risks and dangers for drinking water when inappropriately disposed of.

If one looks at the costs arising from the initiatives within the behaviour-related strategy compared to those associated with technical solutions (drinking water treatment/sewage treatment, Püttmann et al. 2008) or compared to changes in the development of drugs (Kümmerer and Schramm 2008), it becomes clear that the necessary investment is within a relatively modest range. The cost of communication measures in the area of "awareness of the problem among doctors and pharmacists" (seminars, ongoing training) is estimated at approximately 5 million Euros over a 30-year period. Corresponding mass-audience education campaigns about the disposal of medicines can also be conducted on a comprehensive and ongoing basis with approximately 10−15 million Euros.[11] However, one cannot be certain about the costs that would arise as a result of introducing eco-classification and a recommended list. It is difficult to estimate the costs of amending and expanding the reverse logistics for old medicines for pharmacies since we do not know the current costs of this for drug manufacturers in Germany.

10.6 Recommendations and Outlook

Despite all the difficulties inherent in estimating the costs and effectiveness of the initiatives under discussion, one can summarise as follows: some initiatives can be implemented in the short-term, as a precaution to counteract the risk presented by drugs entering drinking water. This especially applies to initiatives that

[10] A total of 24.4 billion DDD were sold in Germany in 2005 (Schwabe and Pfaffrath 2006).

[11] Here we drew upon the cost of other comparable (national and long-term) PR campaigns about sustainable consumption.

can relatively easily be financed and implemented from an organisational point of view. Initiatives that manifest synergies with the health reform can also be tackled in the short to medium term; this might include health promotion, such as the "activity prescription". Due to possible misunderstandings about the "healing priority", protecting people's drinking water should not be communicated as the primary objective.

The example of conflicting information about how one should dispose of old medicines makes it clear that there is immediate need for action here, and corresponding PR campaigns can be deployed in the short term to tell consumers that drugs should never be disposed of via the sewage system.

On the other hand, in addition to the obvious optimisation and resolution of the disposal issue, one should not lose sight of the fact that the percentage of inappropriate disposal constitutes the minor part of drug residues entering the sewage system. It would thus be an important step in the short to medium term to initiate a debate to this effect amongst doctors and pharmacists. The lack of validated knowledge about the impact on humans of drug residues in drinking water means that acceptance of further initiatives which might have stronger implications for laws relating to the environment, waste disposal, and medicines can only be created via a relevant debate.

Acknowledgment The authors would like to thank Barbara Birzle-Harder for her crucial support in carrying out the empirical studies and drafting the behaviour-related initiatives that are presented in this chapter.

References

Apoteket AB (2006) Pharmaceuticals in the Environment (Original title: Läkemedel och miljö). In: Bengtsson B, Gunnarsson B, Wall T, Wennmalm A (eds.) Stockholm, URL: www.janusinfo.se/imcms/servlet/GetDoc?meta_id=8643 (28.11.06)

Ärzte Zeitung (2002) Kosten in Milliardenhöhe durch Non-Compliance. Online-Ausgabe 15.03.2002

Bayerisches Landesamt für Umwelt, Abfallinformationsstelle (2006) Abfallratgeber Bayern. Altmedikamente. Fachdatei, München

Bertelsmann-Stiftung, Universität Bremen (ed.) (2006) Anreize zur Verhaltenssteuerung im Gesundheitswesen. Effekte bei Versicherten und Leistungsanbietern. Chartbook, Gütersloh.

BLAC (Bund-Länderausschuss für Chemikaliensicherheit) (2003) Arzneimittel in der Umwelt. Auswertung der Untersuchungsergebnisse, Hamburg.

Bronder E, Klimpel A (2001) Unused drugs returned to pharmacy – new data. Int J Clin Pharmacol Ther 11, 480−483

Bundesministerium für Gesundheit (2007) Das Glossar zur Gesundheitsreform. http://www.die-gesundheitsreform.de/glossar/fortbildungspflicht_fuer_aerzte.html, 28.11.2007

Dürr M, Hollert H (2007) Arzneimittel in der Umwelt. Ein durch Unsicherheit und Nicht-Wissen gekennzeichnetes Problemfeld. UWSF – Z Umweltchem Ökotox 3:154

EMEA (European Medicines Agency) (2006) Guideline on the environmental risk assessment of medicinal products for human use. Doc. Ref. EMEA/CHMP/SWP/4447/00. London

Götz K, Keil F (2007) Medikamentenentsorgung in privaten Haushalten: Ein Faktor bei der Gewässerbelastung mit Arzneimittelwirkstoffen? USWF – Z Umweltchem Ökotox 3: 180–188

Gruber J (2006) The Role of Consumer Copayments for Health Care: Lessons from the RAND Health Insurance Experiment and Beyond. Massachusetts Institute of Technology, National Bureau of Economic Research. URL: www.kff.org/insurance/upload/7566.pdf (26.11.2006). Kaiser Family Foundation, Menlo Park, CA

Jobling S, Sheahan D, Osborne JA, Matthiessen M, Sumpter JP (1996) Inhibition of testicular growth in rainbow trout (Oncorhynchus mykiss) exposed to estrogenic alkylphenolic chemicals. Environ Toxicol Chem 2, 194–202

Kümmerer K, Schramm E (2008) Arzneimittelentwicklung: Die Reduzierung von Gewässerbelastungen durch gezieltes Moleküldesign. In: UWSF – Z Umweltchem Ökotox 4

Lamnek S (2005) Qualitative Sozialforschung, Weinheim/Basel

Pauly MV (1968) The economics of moral hazard: Comment. Am Econ Rev 58, 531−537

Püttmann W, Oehlmann J, Schulte-Oehlmann U (2008) Wassertechnische Strategien zur Reduzierung von Gewässerbelastungen durch Arzneimittelwirkstoffe. UWSF – Z Umweltchem Ökotox 4

Robert Koch-Institut/Knopf H, Melchert U (2003) Bundesgesundheitssurvey: Arzneimittelgebrauch. Konsumverhalten in Deutschland, Berlin

Schröder H (2005) Wie viel Arzneimittel ver(braucht) der Mensch? Arzneimittelverbrauch in Deutschland. In: UBA: Arzneimittel in der Umwelt. Zu Risiken und Nebenwirkungen fragen Sie das Bundesumweltamt. Texte 29/05, Dessau, S. 249−251

Schulte-Oehlmann U, Oehlmann J, Püttmann W (2007) Humanpharmakawirkstoffe in der Umwelt – Einträge, Vorkommen und der Versuch ein er Bestandsaufnahme. UWSF – Z Umweltchem Ökotox 3, 168−179

Schulte-Oehlmann U, Oetken M, Bachmann J, Oehlmann J (2004) Effects of Ethinylestradiol and Methyltestosterone in Prosobranch Snail. In: Kümmerer K (Hrsg), Pharmaceuticals in the Environment, Berlin, S. 233–247

Schwabe U, Paffrath D (Hrsg.) (2006) Arzneiverordnungs-Report 2005, Heidelberg

Stockholms Län Landsting (2006a) Environmentally classified pharmaceuticals. Best Practice Information Flyer

Stockholms Län Landsting (2006b) Testing for pharmaceutical residues in waste- and drinking-water. Best Practice Information Flyer

Technikerkrankenkasse (2006) www.tk-online.de/centaurus/generator/tk-online.de/s03_ presse-center/04_fotos/01_themen_a_bis_z/sicherheit/sicherheit_hausapotheke.html (20.11.07)

VfW-Aktiengesellschaft (2002) www.ctm.at/vfw/total.asp?peco=&Seite=208&L g=1&Cy=1& UID= (28.11.2007)

Wennmalm Å (2003a) Management of Pharmaceutical Drug Residues from Public Health Care in Stockholm County Council. In: ENVIRPHARMA Conference Proceedings, Lyon, o.S.

Wennmalm Å (2003b) A Proposed Environmental Classification System for Medicinal Products. In: ENVIRPHARMA Conference Proceedings, Lyon, o.S.

Wennmalm Å, Gunnarsson B (2005) Public health care management of water pollution with pharmaceuticals: environmental classification and analysis of pharmaceutical residues in sewage water. Drug Inf J 39, 291−297

http://www.der-gruene-faden.de (28.11.2007)

http://www.selbstbehandlung.de (28.11.2007)

Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland (2003) Modellversuch – Ausgabe einer vertragsärztlichen Leistungs-und Kosteninformation in der Kassenärztlichen Vereinigung Rheinhessen. Ergebnisbericht der wissenschaftlichen Begleitung (Evaluation), Bonn

Chapter 11
Disposal of Pharmaceutical Waste in Households – A European Survey

Gerald Vollmer

11.1 Pharmaceutical Waste – Reducing the Environmental Burden

Pharmaceutically active compounds are created to have specific physicochemical and biological properties. While such characteristics are necessary to deliver the desired therapeutic effect, many pharmaceutical products have an impact on the aquatic environment (comprehensive information on sources, fates and effects in K Kümmerer Pharmaceuticals in the Environment 2008). In an EEA report (European Environment Agency 2010) on "Pharmaceuticals in the Environment" the results on a workshop including proposals for action are summarised.

Not all packages of pharmaceutical products prescribed or bought as over the counter (OTC) are actually taken for therapy. Instead, a considerable number of them are wasted because the therapy succeeds before all tablets are taken, the product's expiry date passes, the expected effect does not occur, or the patient stops the therapy due to side effects and other reasons for insufficient compliance.

The disposal of unused or expired pharmaceuticals is worthy of particular interest. Pouring them into the sink or toilet has a direct impact on the water environment. Some active ingredients cannot be completely removed during waste water treatment and so could appear in drinking water.

The use of methods of "green pharmacy" to create active ingredients that deliver the desired therapeutic effect but have less environmental impact has started but is not yet very common. The priority remains to ensure safe disposal methods for expired and unused pharmaceuticals as this is currently the easiest way to reduce their environmental burden. Combustion in modern waste incinerators should be

G. Vollmer (✉)
European Environment Agency, Copenhagen, Denmark
e-mail: gerald.vollmer@eea.europa.eu

Disclaimer: The results of the questionnaire described here are compiled on the basis of the responses from the national authorities in charge of pharmaceutical waste. Used data are their responsibility.

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_11,

the preferred treatment of pharmaceutical waste (as for other aspects see Castensson and Ekedahl, Chap. 12, this book).

Previous studies have used a variety of questionnaires to assess consumer behaviour on the disposal of pharmaceuticals. However, a comprehensive overview of consumer behaviour, amounts of collected pharmaceuticals, and participation of pharmacies or municipal collection centres in separate collection of waste pharmaceuticals, has been missing. The European Environment Agency (EEA) therefore launched such a Europe-wide questionnaire in 2008 and assessed the results, which are summarized in the rest of this chapter.

11.2 Legislation

Several pieces of EU legislation refer to pharmaceutical waste:

- Commission Decision (2000)/532 (EC) part 2 distinguishes between "pharmaceuticals" and "medicines". Medicines are categorised under waste from health care or as part of the municipal waste (household and similar). For municipal waste, under category 20 01 31 cytotoxic and cytostatic medicines are listed, whereas category 20 01 32 lists all other medicines. Unused or expired cytotoxic and cytostatic medicines are defined as hazardous waste, other medicines not.
- Article 54 (j) of Directive 2004/27/EC (2004) amending Directive 2001/83/EC on the Community code relating to medicinal products for human use requires that "the following particulars shall appear on the outer packaging ... specific precautions relating to the disposal of unused medicinal products ... as well as a reference to any appropriate collection system in place". Article 127b of this Directive refers to collection systems: "Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired".
- Directive 2008/98/EC on waste and repealing certain other Directives states in the consideration No. 17 that "Waste collection schemes which are not conducted on a professional basis should not be subject to registration as they present a lower risk and contribute to the separate collection of waste. Examples of such schemes are waste medicines collected by pharmacies ...".
- The Basel Convention on the Control of Movements of Hazardous Waste (1989) lists in Annex I "categories of wastes to be controlled" under Y3: Waste pharmaceuticals, drugs and medicines.

11.3 The EEA Questionnaire on Disposal of Unused Pharmaceuticals in Households

EEA created a questionnaire which was sent to all national focal points (NFPs) within the European Environment Information and Observation Network (Eionet) of the European Environment Agency. Whereas other questionnaires interviewed

single citizens or contacted associations, this was the first comprehensive survey of human pharmaceuticals waste based on responses from the authorities in Europe responsible for pharmaceutical waste.

The questionnaire focussed on:

- Means of informing citizens
- Classification of pharmaceutical waste
- Take back schemes
- Estimation – as far as available – of the annual amount of collected pharmaceuticals wasted in households

The questionnaire did not include the evaluation of pharmaceutical waste from hospitals for the following reasons. First, the amount of pharmaceutical products purchased by a hospital is close to the real needs – there is little leftover to be wasted. Second, hospitals' pharmaceutical waste usually does not pose an environmental burden as it will be regularly incinerated with other hospital waste.

The questionnaire was sent to the National Focal Points of all EU Member States, as well as to Albania, Croatia, Iceland, Liechtenstein, Norway, Serbia and Switzerland. Out of 34 countries 28 responded, while for the UK replies were received from Northern Ireland, Scotland and Wales only.

11.4 Educating and Informing Citizens

Consumer behaviour regarding the disposal of pharmaceutical waste determines the impact on the water environment. Although all authorities are convinced that unused pharmaceuticals should never be discharged through the sink or toilet, this behaviour is still common.

The means to inform citizens about the best way of disposal varies widely in Europe. Due to cultural differences and national authorities' previous experience of how best to communicate information to citizen, different approaches are used. Very often, cities, counties and regions use their websites to disseminate information. Brochures and leaflets addressed to the consumer are also common. To reach all citizens, the leaflet in Luxembourg for example is issued in five languages.

In some countries there is information on the collection containers placed in a pharmacy or at other places. Other countries rely on direct oral information given by pharmacists or doctors to patients.

Information is also given by associations of pharmacists and by the take back systems for unused or expired pharmaceuticals, e.g. Cyclamed in France.

Because a special collection system for unused pharmaceuticals exists in nearly all EU Member States, the recommendation to return unused or expired pharmaceuticals to a pharmacy or to a special collection centre is a key message.

In the EEA questionnaire we did not focus on differences in type and style of consumer information. In fact, the results presented in Fig. 11.1 show the total effort undertaken to inform the consumer about the correct way of disposal and indicate the number of information sources used.

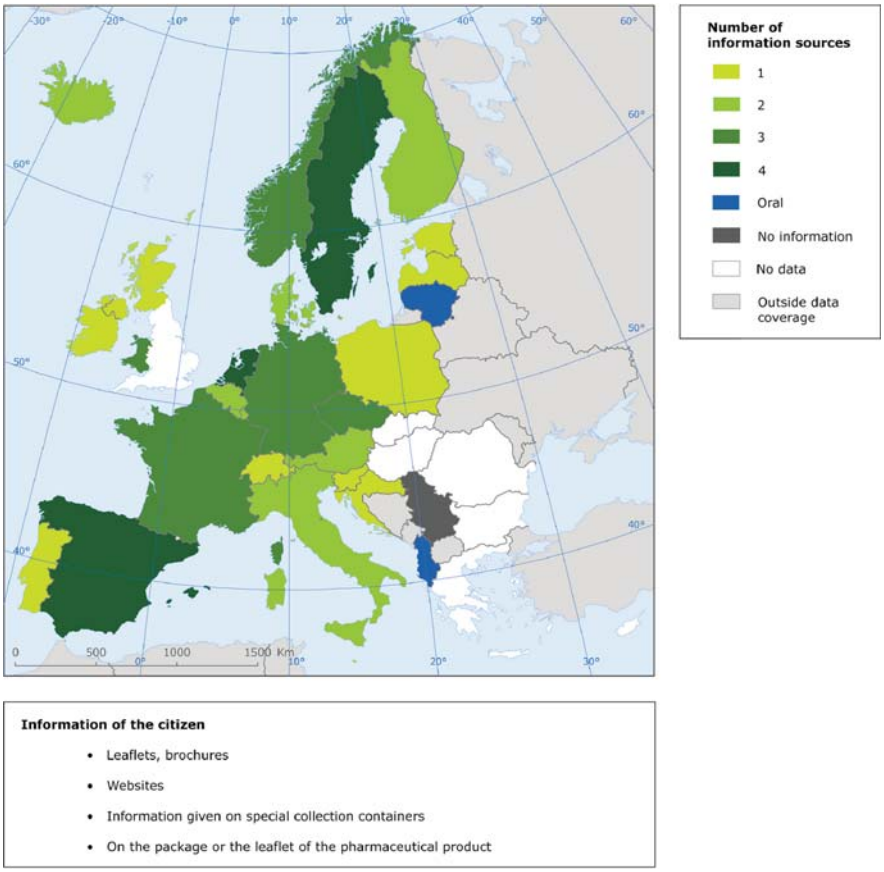


Fig. 11.1 Information provided to citizens on disposal of pharmaceuticals as waste (number of Information sources)

The effort undertaken differs widely. The Netherlands, Spain and Sweden use all means of information provision considered in the questionnaire.

Recommendations from the United States, where a nationwide take-back scheme does not exist, show the efforts needed to reduce the risks for small children. The Missouri Department of Natural Resources (2008) instructs putting liquid or solid medications into a hard plastic container and adding thickening material like cat litter, charcoal or coffee grounds. The riverside county waste management department, California (2008), states that liquid medications must be emptied into paper towels; pills must be crushed and mixed with cat litter or coffee grounds.

Smarxt Disposal, a joint public awareness campaign of the USA Fish and Wildlife Service, the American Pharmacists Association and the Pharmaceutical Research and Manufacturers of America created a video on the complex procedure

of crushing medication and sealing the package which is required before a pharmaceutical can be disposed of in a household bin.

11.5 Amounts of Pharmaceutical Waste

An Europe-wide overview of amounts of unused pharmaceuticals and their return rate does not exist. Data available before the present study was conducted were as follows.

The Government of the Austrian Land Styria (Steiermark) publishes data on unused pharmaceuticals as hazardous waste. For 2004 up to 2007, the amounts vary between 80.4 and 98.9 t/million capita.

In a collection programme using special collection containers in 60 out of 216 pharmacies in the city of Krakow, Poland in 2007, 4,928 kg of unused and expired pharmaceuticals were collected (Krakow Ekocentrum 2008). On that basis one the city of Krakow's pharmaceutical waste can be estimated at 25 t/capita/year. Liquid pharmaceuticals and aerosols were excluded.

The altmedikamente initiative estimated that in Germany the Vfw-REMEDICA and of MEDIrecycling take back schemes dispose of 1,400 of the 4,000−7,000 t of pharmaceuticals not used each year. The amount of unused pharmaceuticals collected in France annually by the CYCLAMED system increased from 6,900 t in 1995 to 10,300 t in 1998 per year (Macarthur 2000). For 2007, 13,000 t of unused pharmaceuticals collected in France were reported (Taylor and Poulmaire 2008). The same authors estimate the effectiveness of different return systems for five countries ranging from 1 to 80%.

Isacson and Olofsson (1999) found in the County of Malmöhus, Sweden that 3% of the sold pharmaceuticals were returned for disposal to Pharmacies. Eurostat (2009) provides information on household waste evaluated in 2004 and 2006. Category ewc_02 covers without specification hazardous and non-hazardous "chemicals preparation waste" including pharmaceuticals.

Within the EEA evaluation, the responsible authorities were asked for an estimation of the annual amounts of unused pharmaceuticals returned via special waste collection systems. Twenty state authorities responded (see Table 11.1).

The amounts calculated per capita differ widely. It should be noted that some of the figures are based on exact counting, whereas other figures are estimates (e.g. Germany and Ireland). Some figures are probably based on pharmaceutical waste collected in municipal collections centres without counting the amount from pharmacies and the share given to household waste without further notice.

As the amount of disposed pharmaceuticals depends, among other factors, on the amount distributed, Table 11.1 includes information on packages marketed (data from Ipf report 2008). Following Ipf (2009), the data for Austria can be taken for Styria. Figures for France show a high amount of distributed packages. The return rate in Switzerland seems to be higher as in all other countries. However, Fig. 11.2

Table 11.1 Annual pharmaceutical sales and waste per capita (total waste including packages)

Country	Sold packages (per capita annually)	Waste (g per capita annually)
Croatia	-	0.19
Estonia	19.46	3.4
Slovenia	16.91	4.5
Lithuania	27.12	10
Finland	16.64	11
Iceland	-	19
The Netherlands	14.34	30
Czech Republic	25.75	36
Liechtenstein	-	39
Belgium	21.83	46
Italy	28.87	54
Denmark	14.84	55
Spain	26.99	57
Portugal	25.12	58
Germany	18.34	73
Sweden	16.91	119
Ireland	22.86	142
Luxembourg	27.72	174
France	51.79	231
Switzerland	19.78	237
Styria	22.71 (Austria)	99

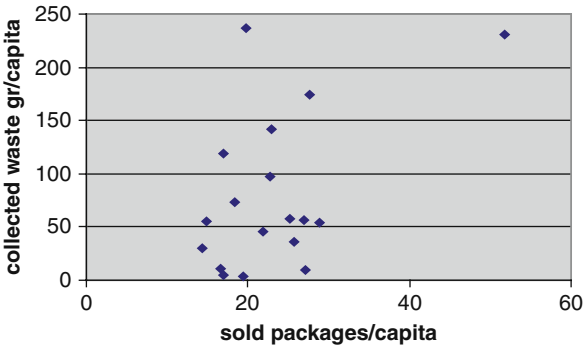


Fig. 11.2 Pairs of values pharmaceuticals sold vs. amount of waste collected

shows that the return rate depends obviously on various elements beyond the amount of pharmaceuticals marketed.

11.6 Classification of Pharmaceutical Waste

How is pharmaceutical waste being categorized: as "normal household waste" or as waste to be collected separately?

Despite its possible effect on wildlife and potentially on small children, pharmaceutical waste is currently not defined as dangerous waste within EU legislation. It should be noted that a study on hazardous household waste (DG Environment 2002) concluded that leather products and pharmaceuticals were household products that cannot be labelled as hazardous but could still potentially pose a risk to health and environment during disposal.

Figures are not available for intoxications of small children by disposed pharmaceuticals. However, the data from tox information centres on consultations give some basic information. The Giftinformationszentrum Nord Göttingen (2007) records in its annual report for 2007, 10,779 cases mainly from northern Germany of consultation after uptake of pharmaceuticals. Out of those, 2,784 (25.8%) are cases concerning small children (aged 1−4). These figures include uptake from all types of sources in the household including waste bins.

The given classification is not valid for cytotoxic and cytostatic medicines, which are defined as dangerous. However, because they are primarily used in hospitals and cancer treatment centres, the EEA evaluation did not target those pharmaceuticals. It should be noted that the trend is more and more out patient treatment, i.e. after 1–2 days in the hospital at the beginning of the therapy patients return home and take their pharmaceuticals there.

Defining waste as "not dangerous" does not necessarily mean that it is preferable to dispose it as normal household waste; e.g. glass bottles are often subject to special collections systems.

Figure 11.3 shows that, with the exception of Malta and Serbia, all countries that responded to the questionnaire classify pharmaceutical waste as subject to special collection systems. Some allow also collection within normal household waste. However, the enormous success of the Cyclamed system in France suggests that the amount of pharmaceutical waste in household waste must be very limited.

Concerning Serbia, the responsible desk officer reported that a new law on waste that is being enacted will contain articles on pharmaceuticals. The Environment Ministry of North Rhine Westphalia issued a leaflet on pharmaceutical waste (NRW 2007) stating "putting old and no longer used pharmaceuticals into the grey bin [i.e. household waste] is not only the simplest and most comfortable way to dispose them but also the most environmentally friendly". This leaflet does not mention the potential risks for small children posed by this disposal procedure. It should be noted that this statement is not supported by the German federal authorities, any of the other 15 German Länder or all communities in North Rhine Westphalia.

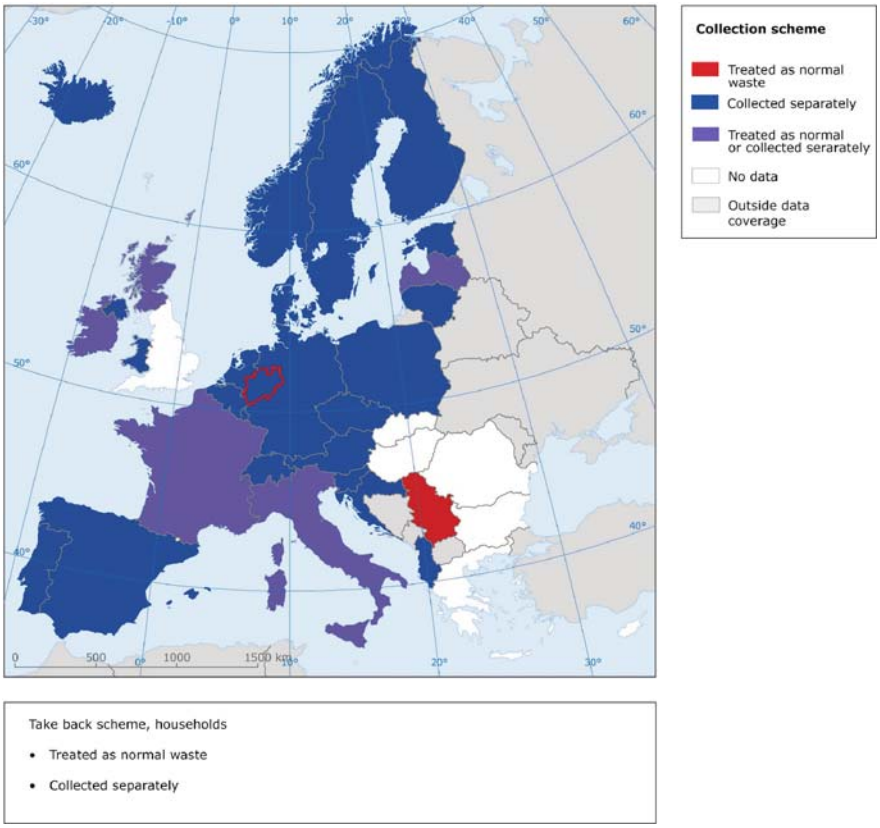


Fig. 11.3 Pharmaceutical waste to be collected as normal household waste or as special waste

11.7 Collection Points for Pharmaceutical Waste

The EEA questionnaire asked those countries where pharmaceutical waste has to be collected separately to identify who was responsible for collecting this special waste.

Figure 11.4 shows that nearly all countries responded that this waste must be given to a pharmacy; some also provided for public collection centres. Only Slovenia excludes pharmacies from its collection programme.

In fact, the majority of European countries have a return scheme for unused and expired pharmaceuticals. Those systems cooperate with pharmacies and take back collected unused or expired pharmaceuticals from there.

In 2007, eight European countries were without a specific unused or expired pharmaceutical return system (Taylor and Poulmaire 2008). This does not mean that those countries do not treat unused pharmaceuticals in a special way. Luxembourg has the "Superdreckskëscht" collection system for dangerous waste which includes pharmaceutical waste. This is taken back in cooperation with the pharmacies. Latvia

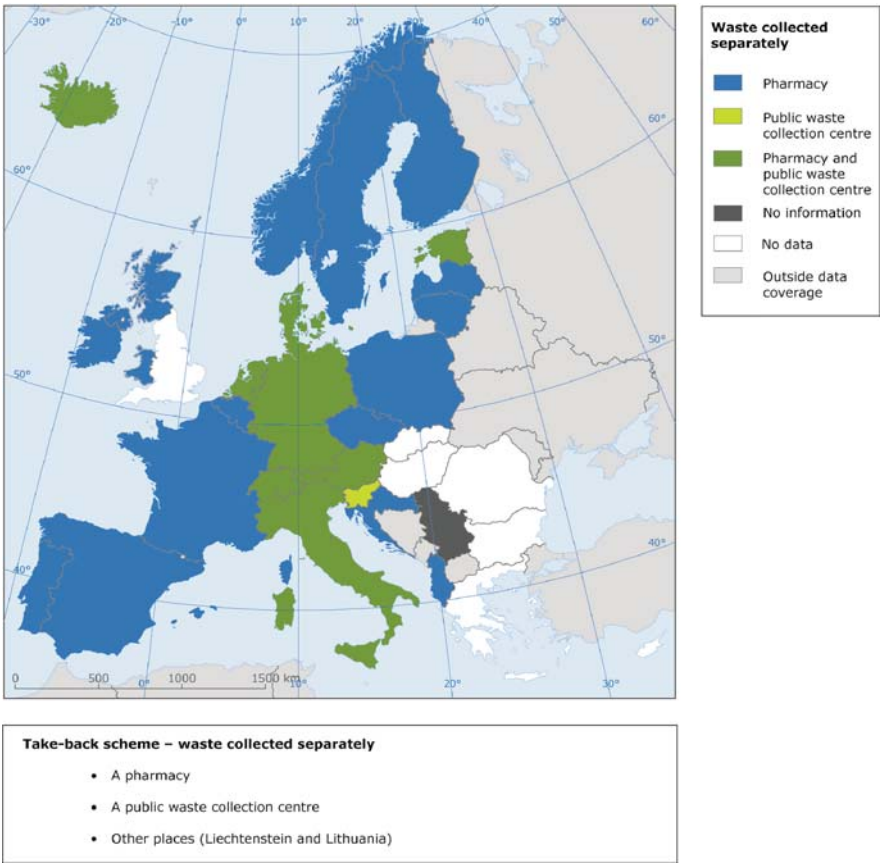


Fig. 11.4 Collections points for pharmaceutical waste provided it is classified as waste to be collected separately

and Slovenia, although lacking a special collection system for unused pharmaceuticals, ask citizens to bring the pharmaceutical waste to public waste collection centres or (in Latvia) to a pharmacy. In Malta, the civic amenity sites collect medicines amongst other waste (WasteServe Malta Ltd). In the United Kingdom unused pharmaceuticals must be given back to a pharmacy. Municipal collection centres are not allowed to collect them.

11.8 Consumer Behaviour and Return Rate

Due to lack of awareness of the environmental consequences or unwillingness to use the collection scheme available, some consumers flush unused pharmaceuticals through the sink or toilet. Götz and Keil (2007) found in a survey in Germany that 16% of people always or at least occasionally dispose of unused or expired tablets

via the toilet. For liquid pharmaceuticals, the authors found that the behaviour is different; 43% of unused or expired drops and syrups are always or at least occasionally discharged through the sink or toilet.

Liquids are an important part of the pharmaceutical market. Sigre (2006), the Spanish return system, reported for Spain that 20% of the pharmaceutical therapeutic units are liquids (solutions, suspensions or similar). Some of those consumers who pour liquid pharmaceuticals down the drain rinse – with best intentions – the emptied syrup bottles with tap water and give them to the glass recycling system.

Persson et al. (2008) reported the results of three surveys (conducted in 2001, 2004 and 2007) among Swedish people. With respect to the question "how would you handle unused prescription drugs?" the response "I would flush it down the drain" declined from 2% in 2001 to zero in 2007. The return rate to the pharmacy increased from 70% in 2001 to 73% in 2007. There is an increasing awareness of the effects of pharmaceuticals on the environment. In 2007, 42% said they were worried, 33% in 2001. During the same period of time, the group which did not worry decreased by 10%.

Bound and Voulvoulis (2005) carried out a survey in south-east England and found that 12% of the population emptied unwanted pharmaceuticals into the sink or toilet. Kruopienė and Dvarionienė (2007) report that in Lithuania 8% of town residents and 6% of those in the suburbs and settlements flush medicines with the sewage. Ruthoy and Daughton (2007) used data collected from the Clark County Coroner's Office, Nevada (USA) and calculated that more than 92% of the medications found at decedent sites were flushed into the sewage system.

A guess of the Umweltbundesamt, Berlin, is that in total about 30% of sold amounts are not used and thrown away. A survey within the START project (2008) based on 1,306 interviews in Germany found that 34% never return their unused pharmaceuticals to a pharmacy; the others return always or at least occasionally unused or expired pharmaceuticals to a pharmacy. Less than one-third of those interviewed always return their unused pharmaceuticals to a pharmacy. Bound et al. (2006) assessed the link between people's attitudes to the environment in general and their attitude to the disposal of drugs based on a survey carried out in South-East England. Only 21% of the people who strongly agreed with the statement: "I live an environmentally friendly life" disposed of pharmaceuticals in the bin, whereas approximately 57% of those people returned them to a pharmacy. Those who neither agree nor disagree with this statement disposed in the bin 75%, and to a pharmacy approximately 22%, of their unused pharmaceuticals. See also Sect. 1.1.6 and Chap. 29 in Kümmerer, Pharmaceuticals in the Environment (2008).

In some countries, home-burning of household waste is a common procedure. Kruopienė and Dvarionienė (2007) found in a survey that 50% of countryside residents in Lithuania dispose of unused medicines by burning them.

In the United States, where a nationwide take back scheme does not exist, Glassmeyer et al. (2009) determined that 35% of unused medication is discharged via the toilet or sink. Seehusen and Edwards (2006) carried out a survey with 301

patients at an outpatient pharmacy; 54% responded that their prior practice was flushing down a toilet unused and expired pharmaceuticals. In a survey based on 500 callers to the Pittsburgh poison information center, Kuspis and Krenzelok (1996) found that 1.4% returned medications to a pharmacy, 54% disposed of them in the garbage and 35% flushed their medications down the toilet or sink.

Statistics Canada (2008) found in a survey of households that 39% disposed of leftover or expired medication using uncontrolled methods like regular household garbage, flushing it down the drain or burying it.

11.9 Participation of Pharmacies as a Legal Duty?

As part of our questionnaire, the responsible authorities were asked whether pharmacies were legally obliged to participate in take back schemes.

The following countries defined a legal obligation of pharmacies to participate in a take-back scheme:

- Belgium
- Croatia
- Denmark
- Estonia
- France
- Iceland
- Lichtenstein
- Lithuania
- Norway
- UK

For UK see also PSNC (2007).

In addition, 16 other European countries call on pharmacies to participate voluntarily:

- Albania
- Austria
- Czech Republic
- Finland
- Germany
- Ireland
- Italy
- Latvia
- Luxembourg
- Netherlands
- Poland
- Portugal

- Slovenia
- Spain
- Sweden
- Switzerland

11.10 Conclusions

Using the National Focal Points within the EIONET network to complete the questionnaire proved to be an effective means to obtain data on pharmaceutical waste that was not previously available.

Collection rates of unused or expired pharmaceuticals in Europe differ widely. They depend on the amount of pharmaceuticals distributed, variance in patients' compliance to use the prescribed pharmaceuticals for therapy and lack of knowledge of established return schemes or the environmental effects of pharmaceuticals flushed into the drain.

Return schemes via pharmacies are well established in most European countries. There seems little need to oblige pharmacies by law to participate in a take back scheme. In many countries where a considerable amount of pharmaceutical waste is taken back, pharmacies participate voluntarily.

The results of the START project (2008) and literature show that there is uncertainty among citizens about proper waste disposal of unused pharmaceuticals. The German Advisory Council on the Environment (2007) notes that: "medicines should be clearly labelled on the packaging, together with a warning that pharmaceutical residues should not be disposed of via the sewerage system, but should instead be submitted to a pharmacy for disposal". If unused pharmaceuticals are merely classified as "normal household waste", some consumers will have little understanding of why pharmaceuticals, notably syrups, suspensions or drops, should not be discharged through sink or toilet. An unambiguous policy on pharmaceutical waste disposal is required to clarify consumer uncertainties.

In addition, small children have a natural curiosity to examine things within their reach: coloured pills attract their interest. Pharmaceuticals not intended for the therapy of small children pose a potential risk for them. Return pathways should in all instances be out of the reach of small children.

There is a common understanding that pharmaceutical waste needs special care. In fact, objective 12 of the Commission Communication on Safe, Innovative and Accessible Medicines (2008) states that: Measures to reduce the potentially harmful impacts of pharmaceuticals on the European environment and public health should be proposed.

The hazardous nature of many pharmaceutical wastes is not defined in legislative texts. Nevertheless, most countries have defined unused and expired pharmaceuticals as "dangerous", "harmful", "hazardous", "special waste" or "problematic waste" in recognition of their special status.

References

Altmedikamente, Medikamentenrückstände gefährden Gewässer und Boden, [homepage on the internet] [cited 24 March 2009] www.altmedikamente.com/texte/hintergrund.htm

Bound JP, Voulvoulis N (2005) Household disposal as a pathway for aquatic contamination in the United Kingdom. Environ Health Perspectives 113, 1705−1711

Bound JP, Kitsou K, Voulvoulis N (2006) Household disposal of pharmaceuticals and perception of risk to the environment. Environ Toxicol Pharmacol 21, 301−307

Commission Decision 2000/532(EC) of 03 May 2000 establishing a list of hazardous waste, OJ L 226 pp. 003−024

Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions (2008) Safe, Innovative and Accessible Medicines: A Renewed Vision for the Pharmaceutical Sector, 10 December 2008, COM (2008) 666 final

Cyclamed [homepage on Internet] [cited 02 April 2009] www.unpf.org/cyclamed/

DG Environment (2002) Study on hazardous household waste (HHW) with a main emphasis on hazardous household chemicals, Report No.: CO 5089-2

Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use OJ L 331, p. 0067

Directive 2004/27/EC of the European parliament and of the Council of 31 March 2004, OJ L 136, pp. 0034–0057

Directive 2008/98/EC of the European parliament and of the Council of 19 November 2008 on waste and repealing certain Directives, OJ L 312, pp. 003–027

European Environment Agency (2010) EEA Technical Report 1/2010, Pharmaceuticals in the Environment, ISSN 1725–2237

Eurostat (2009) Data on generation of waste in households, ewc_02 chemicals preparation waste for 2004 and 2006

German Advisory Council on the Environment (2007) Pharmaceuticals in the Environment, Statement No 12, ISSN 1612–2968

Giftinformationszentrum Nord Göttingen (2007) Jahresbericht 2007 [cited 31 March 2009] www.giz-nord.de/giznord/jabe/07/jabe07d.pdf

Glassmeyer ST, Hinchey EK, Boehme SE, Daughton CG, Ruhoy IS, Conerly O, Daniels RL, Lauer L, McCarthy M, Nettesheim TG, Sykes K, Thompson VG (2009) Disposal practices for unwanted residential medications in the United States. Environ Int 35, 566−572

Götz K, Keil F (2007) Drug disposal in private households: does the disposal of pharmaceuticals via domestic sanitary devices contribute to water contamination? Z Umweltchem Ökotox 18, 180−188

Ipf report (2008) E Walter, Institut für pharmaoekonomische Forschung, quoted in [cited 23 March 2009] http://www.apotheker.or.at/internet/oeak/ZDF_1_0_0a.nsf/d1b453f51450a72dc1256a7d0052b989/. . ./$FILE/Kapitel4

Ipf (2009) Oral information by E. Walter

Isacson D, Olofsson C (1999) Drugs up in smoke: a study of caseated drugs in Sweden. Pharm World Sci 21(2), 96−99

Kümmerer K (2008) Pharmaceuticals in the environment. 3rd edition. Springer, New York

Kuspis DA, Krenzelok EP (1996) What happens to expired medications? A survey of community medication disposal. Vet Hum Toxicol 38(1), 48−49

Krakow Ekocentrum (2008) Zbiórka przeterminowanych leków w aptekach, [homepage on the internet] [cited 30 March 2009] www. ekocentrum.krakow.pl/ZbiorkaPrzeterminowanychLekowW.html

Kruopienė J, Dvarionienė J (2007) Pharmaceutical pathways to the Environment in Lithuania. Environ Res Eng Manag 3, 33−39

Macarthur D (2000) Any old drugs? Two schemes for the disposal of unwanted medicines in Europe. Pharm J 264, 223−224

Missouri Department of Natural Resources (2008) Proper disposal of household pharmaceutical waste [cited 30 March 2009] www.dnr.mo.gov/pubs/pub2291.pdf

National focal points of the European Environment Agency, NFP/EEA [cited 30 March 2009] www.eea.europa.eu/about-us/countries-and-eionet/list-of-members-of-the-nfp-eionet-group

NRW (2007) Ministerium für Umwelt und Naturschutz, Landwirtschaft und Verbraucherschutz des Landes Nordrhein-Westfalen: Alte Arzneimittel richtig entsorgen, 2. aktualisierte Auflage, [homepage on the internet] [cited 30 March 2009] www.munlv.nrw.de

Persson M, Sabelström E, Gunnarson B (2008) Handling of unused prescription drugs – knowledge, behaviour and attitude among Swedish people, Environment International article, in press

PSNC (2007) Pharmaceutical services Negotiating Committee of UK, Essential Services: Waste Management, [homepage on the internet] [cited 30 March 2009] www.psnc.org.uk/pages/essential_services_waste_management.html

Riverside county waste management department, California (2008) Waste Fact Sheet, [cited 24 March 2009] www.rivcowm.org/hhw/fact_sheets/Phamarceutical-2008-09.pdf

Ruthoy IS and Daughton CG (2007) Types and quantities of leftover drugs entering into the environment via disposal to sewage – revealed by Coroner records. Sci Total Environ 388:137−148

Seehusen DA, Edwards J (2006) Patient practices and beliefs concerning disposal of medications. J Am Board Fam Med, 19, 542−547

Sigre (2006) 28001 Madrid, Memoria de actividades 2006, http://www.sigre.es/docs/Memoria_de_actividades_SIGRE_2006.pdf

Smarxt Disposal [homepage on the Internet] www.smarxtdisposal.net – video on safe disposal of medicines [cited on 31 March 2009]: http://www.youtube.com/watch?v=5Tbo2jj8qlc

Start Project (2008) Humanarzneimittelwirkstoffe: Handlungsmöglichkeiten zur Verringerung von Gewässerbelastungen ISOE GmbH, August 2008 [home page on the internet] [cited 30 March 2009] www.start-project.de

Statistics Cananda (2008) Study: disposal of household special waste, March 27, 2008, [cited 30 March 2009] www.statcan.gc.ca/daily-quotidien/080327/dq080327b-eng.htm

Steiermark, Kommunale Abfallerhebung Problemstoffe/Altmedikamente 2004–2007 [cited 31 March 2009] http://app.abfallwirtschaft.steiermark.at/awis_graph/ausgabe/tabelle.php?gr=3&jahr_von=2004&jahr_bis=2007&verband=99&hauptfraktion=7&fraktion=42

Superdreckskëscht, Luxembourg collection system for dangerous household waste, [homepage on the internet] [cited 30 March 2009] www.superdreckskescht.lu/StuffLex/pdfs/Medikamente%201d.pdf

Taylor D, Poulmaire M (2008) An initial survey of unused and expired medicine take-back schemes in the European Union, Conference: pharmaceutical products in the environment: trends towards lowering occurrence and impact. KNAPPE International Conference. Nimes, France (2008)

Vfw-REMEDICA [homepage on Internet] [cited 02 April 2009] www.vfw-gmbh.eu/de/

WasteServe Malta Ltd [homepage on Internet] [cited 30 March 2009] http://wasteserv.gomalta.net/main.asp?ID=21

Chapter 12
Pharmaceutical Waste: The Patient Role

Staffan Castensson and Anders Ekedahl

12.1 What Makes Pharmaceutical Waste a Problem?

The manufacture and use of pharmaceuticals will always be connected with the generation of various categories of waste containing active pharmaceutical ingredients (APIs) and excipients, their transformation products and unwanted by-products. The release of these often highly biologically active chemicals into the environment must be controlled to prevent unacceptable consequences to the environment or to people's health.

The waste and disposal problems start with the production of APIs and end with the final disposal of pharmaceutical products. Pharmaceutical waste is not exclusively an environmental issue. The waste is also part of many peoples' working conditions regarding how it is handled, contained and disposed of. When the material entails serious hazard it requires special handling to ensure safety to people and the environment. Where there are issues with higher risk products, e.g. controlled drugs, increased security in the handling of pharmaceutical waste is also required. A general review of the handling and disposal problems of finished pharmaceutical products in the EU and USA, irrespective of being used or unused, has been published recently (Castensson 2008).

It has been reported that point sources, such as the discharge of process waters from certain manufacturers of APIs, will result in effluent concentrations of pharmaceutical substances from waste water treatment plants well above 1 mg/l (Larsson et al. 2007). The reported measurements revealed six fluoroquinolones at concentration levels above 0.1 mg/l. These levels of antibiotics are known to be toxic to microorganisms and will affect the local environment, including microbial ecosystems. The greatest concern connected with the release of antibiotics into the environment is an accelerated rate of microbial resistance development. A resistance, developed anywhere in the world, may propagate within the biological

S. Castensson (✉)
R&D Department, National Corporation of Swedish Pharmacies (Apoteket AB), SE-118 81 Stockholm, Sweden
e-mail: staffan.castensson@apoteket.se

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_12,

systems and also be carried globally. This should be a strong incentive to reduce emissions of antibiotics independent of the source.

Although the use and the following excretion of pharmaceutical substances or their metabolites appears to be the most serious environmental risk from pharmaceuticals, proper waste management and the minimisation of hazardous pharmaceutical waste will be beneficial. Effective environmental management can be performed at all stages in the life cycle of pharmaceutical products starting with the manufacturing of the API. The environmental risk will be reduced by removing unnecessary sources of emission, and thus the cost of disposal can be minimised. Discarded drugs ending up in landfills should be avoided and pollution via landfill effluents should be reduced by implementing protective barriers and separate treatment of landfill leachate (Metzger 2004).

Medicines management embraces the complete drug use process from prescribing to patient use. After finishing a course of treatment, patients may find themselves sitting with unwanted or leftover drugs. The reasons for generation and the management of pharmaceutical waste by the patient are complex and multifaceted problems. Unwanted or leftover drugs arise from both the patient and the prescriber as well as from the design of the pharmaceutical product. A comprehensive list of reasons has recently been published by Daughton and Ruhoy (2008). This chapter will review the international knowledge base surrounding the role of the patient in the generation of pharmaceutical waste.

One important issue of sustainable pharmacy is rational drug use, where the waste of medicines frequently represents the end-point of sub-optimal drug use. Unused medicines have a direct cost to society in a number of different ways, not just as waste. First, they typically represent a sales value in the range of 5–10% of total spend, which is in conflict with rational medicines management. Second, because of their value, they may invite improper self-medication and sometimes illicit use that may lead to health problems and even admission to hospital because of poisoning or treatment failure. Third, all leftover medicines are a safety risk for children and some elderly people. To summarise, the principles of rational drug use aiming at sustainable pharmacy has the objective to obtain both economic and health benefits. The partial utilisation of drugs and the potential use of remaining portions that have expired not only endanger patients but may also raise the cost of health care.

12.2 Proper Pharmaceutical Waste Management

The pharmaceutical waste stream connected to the use of pharmaceuticals in primary care incorporates both used and unused medicines. Proper pharmaceutical waste management by the patient is imperative to protect people and the environment. A cross-sectional review of the pharmaceutical management situation in the EU and USA has shown that definitive and consistent guidance is not yet available (Castensson 2008). The review includes a summary of the actions that European pharmacies are taking in the collection of leftover medicine and shows that formal

product return schemes of leftover drugs are operative in 20 European countries in 2007. Lynch and McCullough (2008) discussed the collection and disposal of unwanted medication in the USA and proposed what pharmacists can do to reduce the burden of this problem. A comprehensive disposal program is also in operation in Canada (Nguyen et al. 2002).

A recent study report from Santa Barbara County in USA by Kallaos et al. (2007) provides information and solutions to the pharmaceutical waste management issue. The report includes a comprehensive review of the scientific literature, an assessment of disposal practices and sentiments, and an evaluation of several actions that could be implemented. The home page of Illinois-Indiana Sea Grant, Habitats and Ecosystems is a valuable resource site for available knowledge and practice. Two well-established but different schemes for the disposal of unwanted medicine in Italy and France are described by Macarthur (2000). Current waste management programs and procedures are published on the web for UK (Essential Services: Waste Management), France (Cyclamed®), Spain (Sigre®), Portugal (Valormed®), Australia (RUM), and Canada (Medications Return Program). The specific problems related to the disposal of controlled drugs in the USA are examined by Herring et al. (2008), who have also published an international review. With an objective to promote proactive actions tied more closely to the end user, Daughton (2003) discusses a wide range of actions that could be implemented in support of a sustainable pharmacy approach.

12.3 Objective and Methodology of This Review

When medicines are wasted, much is lost to society and patients. The problem has been highlighted by several authors, especially in parts of the former Greater Britain, Germany and the Nordic countries. In recent years more countries have joined the research. Many studies have been performed to determine the character of waste and elucidate the patient role. In this chapter, we aim to provide a thorough review of the international knowledge base and analyse the evidence. The results of the studies found are summarised in nine tables showing countries in descending order of population and most recent research.

Studies on leftover or unwanted medicines returned to pharmacies were identified: (1) through searching Medline, Google scholar and Pharmaceutical Press with multiple terms and combinations of keywords – after an initial test the keywords destruction, expired, outdated, recycling, residual, reuse, take-back, and unused were discarded in favour of more useful combinations: pharmaceutical waste, drug waste, medicine waste, medication waste; disposal of drugs, disposal of medicine, disposal of medication; leftover drugs, leftover medicine, leftover medication; returned drugs, returned medicine, returned medication; unwanted drugs, unwanted medicine, unwanted medication; (2) by personal communication with researchers within the field; (3) by scrutinising the reference lists for additional references not identified via (1) and (2).

All references were examined to identify papers fulfilling the inclusion criteria by checking the abstracts or the full text. The eligibility criterion for all studies was publishing/presentation after 1st January 1991. Studies concerned with left-over or unwanted medicines returned to pharmacies including ≥500 returned items or ≥100 patients were eligible for this review. Studies with data from campaigns such as Disposal of Unwanted/Unused Medicines and Poisons (D.U.M.P.) were included but the result of these cannot be correlated directly with available figures of drugs sold. The eligibility criterion for measurements by questionnaire or interview was the inclusion of ≥100 respondents.

12.4 Pharmaceuticals Wasted

Drug disposal regulation or guidance is fragmented at national and international levels; both formal and informal guidance aims to reduce the risks of leftover and unwanted medicine. Most current regulations focus on two security concerns: (1) the disposition of controlled substances and (2) keeping medication away from children.

In this section we centre on descriptive studies elucidating (1) the knowledge and attitudes of the public about purposeful disposal and (2) the patterns of pharmaceuticals returned to pharmacies. In some countries, free samples distributed to medical practices constitute an unknown fraction of overall disposed pharmaceuticals.

12.4.1 How Are Pharmaceuticals Disposed of ?

The methods of disposal has been studied by asking the public or patients about their knowledge and attitudes to leftover and unwanted drugs. Altogether we have found 16 studies fulfilling the inclusion criteria and these are summarised in Table 12.1.

Generally, it can be concluded that "saving for later" consumption or disposal has high preference. Disposal of drugs into the sewage system is probably the least desirable method of disposal and results indicate that this is still common practice in Germany, UK, Canada and USA. Collection at local pharmacies and reverse distribution (using the supply chain in reverse) combined with controlled incineration are advancing in most countries. Holland and the Scandinavian countries are showing return figures of about 60% or more. Reverse distribution is also preferred by respondents who were asked to propose suitable alternatives for disposal of leftover drugs. The same preference is registered also in countries where amounts returned are low.

12.4.2 Type and Volume of Disposed Pharmaceuticals

Measurements of the quantity of drugs that is discarded in proportion of total sold are not available. The best estimates identify a range of 5–10%. Actual survey data

Table 12.1 Disposal of leftover and unwanted drugs; distribution of knowledge and attitudes among respondents

Country References	*n* [a]	Return to a pharmacy (%)	Return to health care (%)	Turn in to hazardous waste station (%)	Dispose of in the garbage (%)	Flush down the toilet or sink (%)	Recycling (%)	Give it to someone else (%)	Save (%)	Other/no answer (%)
USA										
Seehusen and Edwards (2006)	301[b]	23	14			54 (toilet) 35 (sink)		11	54	
Kuspis and Krenzelok (1996)	500[c]	1			54	35				7
Germany										
Götz and Keil (2007)[d]	2,000					10[e] 32[f]				
UK										
Mackridge and Marriott (2006)	404/1,000	38	2		34	16				
Bound and Voulvoulis (2005)	185/392[g]	22			63	12		4	31	
Sullivan and George (1996)	188/400	34[h]			15	27			15	9
Woolf and Scott (1995)	2,082	16			50				20	14
Holland										
Blom et al. (1996)	2,154	58		16		3	9		6	

Table 12.1 (continued)

Country References	n [a]	Return to a pharmacy (%)	Return to health care (%)	Turn in to hazardous waste station (%)	Dispose of in the garbage (%)	Flush down the toilet or sink (%)	Recycling (%)	Give it to someone else (%)	Save (%)	Other/no answer (%)
Canada										
Compas (2002) [i]	1,512				39	20				40
Compas (2002) [j]	1,512				50	19				29
Sweden										
Boije (2007) [i]	226/1,000	43 (73[k])			3				55	1
Boije (2004) [i]	243/1,000	42 (67[k])	1	1	3				54	1
Boije (2001) [i]	231/1,000	41		1	7				48	2
Norway										
ECON (2002)	5,516	69								
Kuwait										
Abahussain and Ball (2007)	200				97	2		0		2
Abahussain et al. (2006)	300[b]				77	11		9		12

[a]Number of respondents/Total selected.
[b]Customers visiting a pharmacy.
[c]People phoning Pittsburgh Poison Center for consultation.
[d]Aggregation of response alternatives sometimes, often and always.
[e]Tablets.
[f]Liquids.
[g]Selection of population unknown.
[h]Include return to health care.
[i]Disposal of R_x.
[j]Disposal of OTC.
[k]Include those saving and that will return the drugs to a pharmacy when judged unwanted.

Table 12.2 Amounts of leftover and unwanted medicine returned to pharmacies

Country References	Sample size, pharmacies	Sample size, packages	Proportion of drugs sold (%)
Germany			
Zimmer et al. (1999)	15	4,351	~5
Heeke and Günther (1993)	195	6,897	5.3
Zimmer et al. (1992)	20	5,760	~5
France			
Marchiset-Ferlay et al. (2001)		10,254	3.6 (value)
UK			
Linton (2003)	18	1,819[a]	0.65 (value)
Cromarty (1998)	60	2,042	0.7 (value)
Sweden			
Ekedahl et al. (2003)	100	20,171	3.8[b] (*DDD*) 2.2 (value)
Agness (2002)	40		5 (value)
Jonsson (2000)	31	1,554	2.4 (value)
Isacson and Olofsson (1999)	65	8,014	2.4 (*DDD*)
Switzerland			
Gehler et al. (1998)	66	10,011	5.5 (packages)
Denmark			
Lægemiddelstyrelsen (2003)	28	9,077	1.45 (value)
Norway			
ECON (2002)	25	2,687	~2

DDD = Defined daily doses.
[a]Drugs instead of packages.
[b]Includes drugs without package.

on drug disposal amounts are summarised in Table 12.2 for the proportion retrieved at pharmacies. A wide variation is observed for the proportion of drugs returned when compared with sold drugs. The UK and Denmark report low proportion values while Germany and Switzerland show almost five times higher values. Where several survey data are available, they seem to be consistent and show no change over time. This may reflect the fact that changing habits is a slow process. In the Swedish experience with more than 30 years of collection and campaigning, approximately three quarters of unused drugs (total unused approximates to 5% of drugs sold) are retrieved at pharmacies for controlled incineration.

Data are sparse on returns of therapeutic subgroups compared with drugs sold, but fractions appear to be proportional to the volume sold. No studies that attempt to standardise the returns with respect to age and gender of patients have been identified.

12.4.3 How Much Is Left in the Package After Use and How Old Are Pharmaceuticals that Are Disposed of ?

Quantitative studies of the remains in the packages returned to pharmacy and when they were dispensed have drawn a lot of attention. The data represent a footprint of drug use and provides evidence to understand important drug utilisation issues.

The resolution of fractions left differs greatly between the studies. In Table 12.3 the results shown are aggregated to compare those fractions of greatest interest as well as the proportion of unbroken packages. It is significant that about two thirds of the packages returned contain more than half or two thirds of the original content and that about half of those packages are unbroken.

Table 12.4 presents the results from the studies reporting the time from dispensing until return and Table 12.5 shows returned packages that have exceeded the expiry date. It can be seen that the drugs appear to have been kept longer before returning in those countries where the collection rate is high. In these countries most returned drugs have also passed expiry date.

12.5 The Patient Behind the Wasted Pharmaceuticals

Medicines are not wanted by the consumer for a wide range of reasons. In this section, we review the studies describing the patients that return pharmaceuticals to pharmacies and the factors behind the return. These drug disposal studies have rarely originated from the potential for reduction of environmental harm, but primarily to understand the drug use of the patient and the attributable costs to the consumer and society. Understanding the patient's reasons means elucidating misuse, inappropriate use and non-adherence. In addition, health provision reasons as availability of pharmaceuticals and prevailing insurance systems are strong determinative factors.

12.5.1 Return Patterns of Unwanted Pharmaceuticals

The number of prescriptions per patient tends to increase as the population ages. Several international studies report that a larger proportion of unused medicines are returned by the elderly. This directly correlates to increased prescribing frequency with age. Hoarding or just stockpiling may add to the problem as well as cases of drug misuse. In Sweden a report of one deceased patient's return of unused drugs was that it contained 212 packages of 36 different pharmaceuticals dispensed on 51 occasions over 3 years. The sales value of the drugs returned was ~62,000 SEK (~6,200€). The drugs were prescribed by seven doctors and each medication was only prescribed by one doctor. However, one prescribed drug was missing in the return, an analgesic containing acetylsalicylic acid 500 mg, caffeine 50 mg and codeine 30 mg. The analgesic was redeemed for all 51 prescriptions together with a lot of unwanted medicines apparently to mask the woman's consumption of codeine (Ekedahl 2003).

Table 12.3 Drug left in the packages returned to pharmacies. The table shows the aggregated per cent figures of packages for those sample fractions representing most left and separately the per cent proportion of unbroken packs in the sample

Country References	Sample size, packages	More than half left (%)	More than two thirds left (%)	Unbroken (%)
Germany				
Bronder and Klimpel (2001)	10,603	63		24
Zimmer et al. (1999)	4,351			19
Heeke and Günther (1993)	6,897	75		36
Zimmer et al. (1992)	5,760	57		
Bronder and Klimpel (1992)	5,164	65		31
UK				
Mackridge and Marriott (2007)	3,765			53
Cromarty (1998)				28[a]
D.U.M.P. (1997)	1,733			28
Hepburn et al. (1997)	1,705			32
Hawksworth et al. (1996)	1,091		65[b]	20
Phillips et al. (1995)	4,485			20
Australia				
Longmore et al. (1995)	6,556		67[b]	
Czech Republic				
Kolar et al. (2001)	1,091			34
Sweden				
Ekedahl et al. (2003)	20,171		65	38
Jonsson (2000)	1,554			37
Isacson and Olofsson (1999)	8,014		70[b]	36
Switzerland				
Gehler et al. (1998)	4,969	66		24
Gehler et al. (1998)	5,042	70		32
Denmark				
Lægemiddelstyrelsen/ Danmarks Apotekerforening (2001)	9,077		38[c]	16
Norway				
ECON (2002)	2,687			38
Thormodsen et al. (1997a)	4,860	70		31
Wold and Hunskår (1992)	2,750			11

[a]Plus 2% overfilled packages.
[b]>0.6 left.
[c]>0.75 left.

The statistical distribution of returns to pharmacies is shown in Table 12.6. It can be calculated that 10% of the patients account for 50% of all returned drugs. This is illustrated in Fig. 12.1 based on data from Ekedahl (2006).

Table 12.4 Storage time of drugs before bringing back to the pharmacy; cumulative per cent figures from the latest prescribed packages to the earliest. The fraction of packages >5 or >7 years is presented in the last column

Country References	Sample size, packages	<1 month (%)	<½ year (%)	<1 year (%)	<2 years (%)	<3 years (%)	<4 years (%)	<5 years (%)	<10 years (%)	>5 or >7 years (%)
USA										
Garey et al. (2004)	1,315					63			94	6 (>7)
UK										
Mackridge and Marriott (2007)	3,765			71						
Linton (2003)	1,819[a]		57	69	78			85		2 (>5)
Grant (2001)	3,099		47	63						
Braybrook et al. (1999)	1,428			80	89	93	95			
Cromarty (1998)	2,005	25		74	94					
Hepburn et al. (1997)	1,705	30								
Cook (1996)	631		63[b]	77						
Canada										
Grainger-Rousseau et al. (1999)	1,966							87		
Carter and Coppens (1996)	2,348			53				91		9 (>5)
Australia										
Longmore et al. (1995)	6,556		23	38	56	71	80	86		14 (>5)
Sweden										
Ekedahl (2006)	9,077		16	27	43			74		26 (>5) 8 (>7)
Ekedahl et al. (2003)	11,093		22	35	51	64		80		
Jonsson (2000)	1,554			33	45	54	64	70		

Table 12.4 (continued)

Country References	Sample size, packages	<1 month (%)	<½ year (%)	<1 year (%)	<2 years (%)	<3 years (%)	<4 years (%)	<5 years (%)	<10 years (%)	>5 or >7 years (%)
Isacson and Olofsson (1999)	5,973	8[c]		38[c]	55[c]	67[c]		84[c]	98[c]	14 (>5)
Denmark Lægemiddelstyrelsen/ Danmarks Apotekerforening (2001)			37[d]		64[e]					

[a]Drugs instead of packages.
[b]49% < 3 months.
[c]Plus 2 months.
[d]< 4 months.
[e]< 16 months.

Table 12.5 Packages returned to pharmacies past their expiry date. The table shows the percentage figure of returned packages past expiry date to total packages with expiry date

Country References	Sample size, packages	Returned past expiry date (%)
Germany		
Zimmer et al. (1999)	4,351	71
UK		
Linton (2003)	1,819[a]	8
Collins (2001)	309	17
Braybrook et al. (1999)	1,428	3
Cromarty (1998)	2,005	3
Hawksworth et al. (1996)	1,091	5
Canada		
Carter and Coppens (1996)	2,348	25
Sweden		
Ekedahl (2006)	9,077	61
Ekedahl et al. (2003)	11,093	51
Jonsson (2000)	1,554	45
Isacson and Olofsson (1999)	7,783	48
Bäckström and Olme (1997)	1,159[a]	38
Switzerland		
Gehler et al. (1998)	~4,700[b]	50
Gehler et al. (1998)	~4,200[c]	71
Norway		
Thormodsen et al. (1997b)	3,493	14

[a]Drugs instead of packages.
[b]Calculated R_x sample.
[c]Calculated OTC sample.

The data in Table 12.6 indicate the same pattern when comparing the range and median figures. A few patients, predominantly elderly, are responsible for returning a large proportion of drugs. Another observation is that the older the patient the more unwanted and leftover drugs are generated. These facts are reported in several papers and Table 12.7 summarises observed fractions taking the retirement age as a cut-off point.

12.5.2 Reasons for Unwanted or Leftover Drugs

Pharmacotherapy is a cornerstone of medical practice and medication comes with considerable costs attached. These costs are direct when accounting for the drugs and indirect when leading to morbidity. It is a well-known fact that patients will not

Table 12.6 Distribution of unwanted and leftover drugs returned to pharmacies

Country References	Sample size, patients	Sample size, packages	Range	Median	Mean[a]
UK					
Linton (2003)	897	1,819[a]	1–34	1	2
McGovern et al. (2002)	100	256	1–17	2	3
Braybrook et al. (1999)	529	1,428	1–31		3
Cook (1996)	133	631	1–72	3	5
Hawksworth et al. (1996)	366	1,091	1–27		3
Spain					
Coma et al. (2008)	227	1,176	1–121		5
Canada					
Carter and Coppens (1996)	731	2,348			3
Sweden					
Ekedahl (2006)	1,577	8,795	1–140	3	6
Ekedahl (2003)	191	1,077	1–101	3	6
Bäckström and Olme (1997)	196	1,159[a]	3[b]–30		6
Norway					
Thormodsen et al. (1997a)	641	4,860	1–70		8
Wold and Hunskår (1992)	247	2,750	1–44		11

[a]Drugs instead of packages.
[b]Only drug returns ≥3 were included.

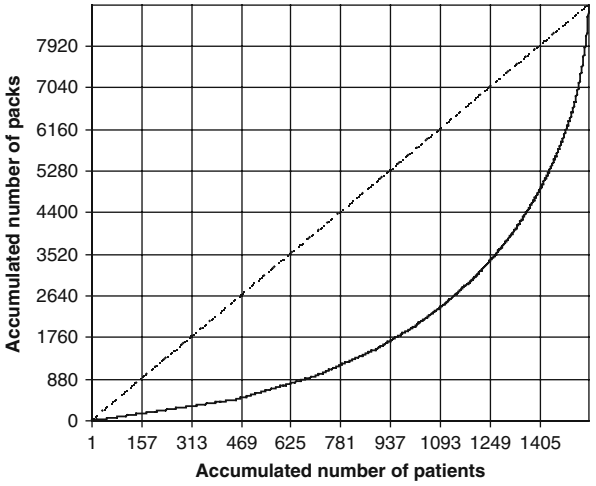


Fig. 12.1 Lorenz diagram ($n = 1{,}557$ patients, 8,795 packs; Gini coefficient = 0.42). The *solid line* represents the real accumulated number of returned packs in relation to accumulated number of patients. The *broken line* is graphically illustrating a uniform return according to the statistical mean (5.65) of returns per patient

Table 12.7 Proportion of patients aged over 60/65 returning unwanted and leftover drugs to pharmacies and proportion of packages returned by these patients. Percentages are tagged 60+ for patient age of 60 years and more and 65+ for 65 years and more

Country References	Sample size, patients	Sample size, packages	Patients (%)	Packages (%)
UK				
Langley et al. (2005)	114	340		61^{60+}
Linton (2003)	897	1,819[a]	65^{60+}	
Braybrook et al. (1999)	529	1,428		67^{60+}
Hawksworth et al. (1996)	360	1,091	61^{60+}	68^{60+}
Canada				
Grainger-Rousseau et al. (1999)	581	1,966		63^{65+}
Carter and Coppens (1996)	731	2,348	$42/44^{65+}$	
Sweden				
Ekedahl (2006)	1,577	9,077		66^{65+}
Ekedahl (2003)	191	1,077	49^{65+}	64^{65+}
Ekedahl et al. (2003)		20,171		66^{65+}
Jonsson (2000)	299	1,554		59^{60+}
Isacson and Olofsson (1999)		8,014		63^{65+}
Bäckström and Olme (1997)	196	1,159[a]	49^{65+}	47^{65+}

[a]Drugs instead of packages.

always take medications according to prescription and begins with the primary non-adherence, which means that patients are not redeeming their prescriptions (Jones and Britten 1998).

People have been surveyed as to why medicines they have obtained had not been taken. This secondary non-adherence was focused in 20 studies based on our inclusion criteria and the study results are summarised in Tables 12.8 and 12.9. The factors that contribute to secondary non-adherence include frequent physician's alterations in dosage of existing drugs and prescribing of new drugs, patient improvement, adverse reactions and that the patient cannot detect whether his/her condition is worsening or improving. In our review of the reasons reported, we have tried to resolve the factors behind secondary non-adherence as seen in Table 12.8. The table reflects primary factors related to the pharmacotherapy generating leftover and unwanted drugs. The non-adherence factor shown in the table reflects the patient's perspective not to take any more medications because of, e.g. fear.

The patient's death is a very obvious reason why leftover drugs are generated because of discontinued drug use. However, the patient will also experience several situations, which can be regarded as secondary factors in relation to the pharmacotherapy that generate leftover and unwanted drugs. These are presented in Table 12.9.

One way to reduce drug waste caused by an early change or discontinuation of treatment is to limit systematically the quantity of medication that is

Table 12.8 Reasons for leftover and unwanted drugs. The table shows the distribution in per cent of primary factors related to the pharmacotherapy. Several factors may be registered by one respondent

Country References	Sample size, patients/ packages	Therapy change	Adverse reactions	No effect	Non-adherence	Recovery
UK						
Mackridge and Marriott (2007)	910/4,934	17			7	
Mackridge and Marriott (2006)	162/	60	21			54
Langley et al. (2005)	114/340	55				
Linton (2003)	897/1,819[a]	33	4	3	5	2
McGovern et al. (2002)	100/256	48	5		7	
Collins (2001)	102/309	33		7	13	6
Braybrook et al. (1999)	529/1,428	44	7		12	
Cromarty (1998)	/2,005	20	4			10
Hepburn et al. (1997)	/1,705					30
Cook (1996)	123/631	24			1	
Hawksworth et al. (1996)	360/1,091	25				
Credé (1995)	/1,825	30	10			
Spain						
Coma et al. (2008)	227/1,176	18	3	3	1	25
Canada						
Carter and Coppens (1996)	731/2,348	20	8		7	11
Holland						
Blom et al. (1996)	477/	25	7	5		
Sweden						
Ekedahl (2006)	1,022/9,077	20	9	6	2	18
Jonsson (2000)	299/1,554	33	11			
Bäckström and Olme (1997)	135/1,159	38	13	7	5	18
Kuwait						
Abahussain et al. (2006)	264/	49			26	
Norway						
Thormodsen et al. (1997b)	353/3,493	23		4		4
New Zealand						
Braund et al. (2008)	126/	37	14	12		

[a]Drugs instead of packages.

Table 12.9 Reasons for leftover and unwanted drugs. The table shows the distribution in per cent of secondary factors related to the pharmacotherapy and unrelated. Several factors may be registered by one respondent

Country References	Sample size, patients/ packages	Expired	Stockpiling	Prescribing error	Deceased	Other factors
UK						
Mackridge and Marriott (2007)	910/4,934	28	1		34	
Linton (2003)	897/1,819[a]	8	1		30	
McGovern et al. (2002)	100/256	1		2	34	
Collins (2001)	102/309	17	8	2	40	9
Braybrook et al. (1999)	529/1,428	3	30[b] 18[c]	4	14	
Cromarty (1998)	/2,005	3		1	33	
Hepburn et al. (1997)	/1,705				26	
Cook (1996)	123/631	20	2		53	
Hawksworth et al. (1996)	360/1,091	5	23		42	5
Credé (1995)	/1,825		10		57	
Spain						
Coma et al. (2008)	227/1,176	28			21	3
Canada						
Carter and Coppens (1996)	731/2,348	25			27	
Sweden						
Ekedahl (2006)	1,022/9,077	22	1		30	
Jonsson (2000)	299/1,554	33	5		14	13
Bäckström and Olme (1997)	135/1,159	19			48	
Kuwait						
Abahussain et al. (2006)	264/	11	10[b] 30[c]			
Norway						
Thormodsen et al. (1997b) [d]	353/3,493	14			50	6
New Zealand						
Braund et al. (2008)	126/	28				

[a] Drugs instead of packages.
[b] Excess/double prescribing.
[c] Greater purchase than need.
[d] Hospitalisation 4%.

initially dispensed. The concept of trial packages or starter packages has been practised in Sweden when starting a new long-term treatment, and has been highly recommended when investigating ways to reduce the costs of leftover drugs (Socialstyrelsen 2004). In Canada, trial prescriptions have been tested by

several public and private-sector organisations. These permit pharmacists to fill new prescriptions for specified long-term medications in two parts – an initial supply and, if the drug is tolerated, the balance. The evaluation by Paterson and Anderson (2002) reported the proportion of patients who received the balance varied by program, ranging from 47 to 87%. The value of the wastage avoided was roughly Can$ 5.50 per trial initiated.

12.6 Sustainable Drug Use

Integration of all aspects of drug use will include the complete medicine process from prescribing to patient. This implies that actions to optimise one aspect of this highly structured process cannot be done in isolation to get the best sustainable drug use outcome – in terms of human health, ecology and economy. The concept of sustainable pharmacy, e.g. to cut away all unnecessary sources of emissions to the environment, is very much an issue of rational drug use. The use of and the subsequent excretion of pharmaceutical substances and their metabolites constitute the most serious environmental risk of pharmaceuticals; however the fact that leftover drugs constitute a significant share and proper management of these is important. Unwanted or leftover drugs arise from factors related to prescribing, dispensing and use, i.e. actions by prescribers, pharmacists and patients, actions that are influenced by the design of drug benefit schemes and the incentives present.

There is a large inter-country variation of how an individual disposes of drug waste and how many leftover drugs are returned to pharmacies. The differences in the patterns of drugs returned to pharmacies (time after purchase, unopened packs, packs past expiry date) reflect attitudes in society as well as actions taken by pharmacists and other professional groups involved in drug use. But there are also differences among patients between attitudes (what should be done) and behaviour (what is done), identifying the need for clear and attractive incentives for prescribers, pharmacists and patients to facilitate proper management of leftover drugs. It seems that the public's awareness of problems arising from drugs in the environment is steadily growing. In addition, surveys in different countries reveal that reverse distribution, e.g. return of leftover drugs to pharmacies, is generally identified as the preferred method for disposal of waste.

12.7 Conclusion

The design and implementation of drug benefit schemes, regulating the patients' cost sharing for drugs, is a crucial aspect surrounding leftover drugs. Drug benefit schemes and/or the structure of the healthcare system may provide perverse incentives to purchases of large amounts and stockpiling of drugs, increasing the waste volume if the therapy is changed or the patient dies.

The reasons for leftover drugs recorded in different countries are similar. Therapy changes due to too little or no effect and due to adverse drug reactions are common, especially when a new drug therapy is initiated. Trial prescription when new drug therapy is instituted is an action that seems worthwhile.

In countries, e.g. Germany and Sweden, where surveys indicate that returns to pharmacy is the major way to dispose of leftover drugs, a higher proportion of drugs sold are returned to pharmacies and drugs past expiry date and purchased long before returning them constitute the majority of the returned drugs. This is in comparison with countries with a lower proportion returned to pharmacies, e.g. UK. The distribution of patients' drug returns is skewed as a small number of patients contribute to the majority of all leftover drugs, which are often disposed of when the patient dies. Efforts to identify and provide pharmaceutical care to those patients and solving their drug related problems may prove beneficial not only for treatment outcomes, but also as a method to reduce drug waste.

Best sustainable drug use outcome – in terms of human health, ecology and economy – implies that actions to optimise all aspects of drug use must be considered. Rational drug use is core to the concept of sustainable pharmacy. Actions for sustainable pharmacy should aim to reduce the unnecessary sources of emissions to the environment, including leftover drugs.

References

Abahussain EA, Ball DE (2007) Disposal of unwanted medicines from households in Kuwait. Pharm World Sci 29, 368–373

Abahussain EA, Ball DE, Matowe WC (2006) Practice and opinion towards disposal of unused medication in Kuwait. Med Princ Pract 15, 352–357

Agness S (2002) Kasserade läkemedel och attityder hos apotekskunder till provförpackningar och synonympreparat. [Disposal of drugs and attitudes of pharmacy customers to trial packages and synonymous drugs] Report Apoteket AB 2002-01-20

Bäckström I, Olme B (1997) Projekt Compliance – Orsak, struktur och volym av återlämnade läkemedel till apoteken. [Project Compliance – Reasons, structure and volume of drugs returned to pharmacies]. Project report. Apoteket AB June 1997

Blom AT, De Bruijn JC, Van de Vaart FJ (1996) How consumers deal with the remainders of unused prescription drugs. Pharmaceutisch Weekblad 131, 102–107

Boije C (2001) Marknadsundersökning. Överbliven receptbelagd medicin. [Market research. Unused prescriptions drugs] 2001-02-22. SIFO Research & Consulting

Boije C (2004) Överbliven receptbelagd medicin. [Unused prescriptions drugs]. Gullers/LIF, SIFO Research International Sweden AB. Pnr 1511677. January 2004

Boije C (2007) Överbliven receptbelagd medicin. [Unused prescriptions drugs]. Gullers/LIF, SIFO Research International Sweden AB. Pnr 1515648. January 2007

Bound JP, Voulvoulis N (2005) Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environ Health Perspect 113, 1705–1711

Braund R, Chuah F, Gilbert R, Gn G, Soh A, Yin Tan L, Shing Tiong H, Yuen Y-C (2008) Identification of the reasons for medication returns. NZ Fam Physician 35, 248–252. [cited 2008 Dec 04]. Available from: http://rnzcgp.org.nz/assets/Uploads/NZFP/Aug2008/Braund_Aug_08.pdf

Braybrook S, John DN, Leong K (1999) A survey of why medicines are returned to pharmacies. Pharm J [serial on the Internet] 263, 7063. [cited 2008 Oct 10]. Available from: http://www.pharmj.com/editorial1999/19990918/pharmacypractice/braybrook2.html

Bronder E, Klimpel A (1992) Der Rucklauf unverbrauchter Arzneimittel. [The return of unused drugs]. Pharm Z 137, 554–556

Bronder E, Klimpel A (2001) Unused drugs returned to the pharmacy – new data. Int J Clin Pharmacol Ther 39, 480–483

Carter BA, Coppens RC (1996) EnviR research project on drug waste in Alberta. Summary report. Alberta Pharmaceutical Association

Castensson S (2008) Pharmaceutical waste. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. 3rd edition, Springer, Berlin, Heidelberg, New York, pp. 551–561

Collins L (2001) The Waste Medicines Survey. CherwellVale Pharmacy Development Group

Coma A, Modamio P, Lastra CF, Bouvy ML, Marino EL (2008) Returned medicines in community pharmacies of Barcelona, Spain. Pharm World Sci 30, 272–277

Compas (2002) F&DA Environmental Assessment Regulations Project Benchmark Survey. A Report to Health Canada (POR-02-13), Office of Regulatory and International Affairs. March 2002. Ottawa, Toronto, Winnipeg: Compas Inc. (PN: 332-04). [cited 2008 Oct 10]. Available from: http://www.hc-sc.gc.ca/ewh-semt/contaminants/person/impact/por-02-13-eng.php

Cook H (1996) Why so many drugs go to waste. Pharm Pract 6, 268, 270

Credé B (1995) How much unused medication was collected by Community Pharmacies in Barking and Havering in 1994/95. Report Barking and Havering Health Authority, The Clockhouse, East St, Barking IG11 8EY

Cromarty E (1998) A review of drug wastage in primary care. Report October 1998. Grampian Area Pharmaceutical Committee, United Kingdom

Cyclamed [homepage on the Internet]. [cited 2008 Oct 1]. Available from: http://www.unpf.org/cyclamed/video_index2.htm

Daughton CG (2003) Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions. Environ Health Perspect 111, 775–785

Daughton CG, Ruhoy IS (2008) PharmEcovigilance: Aligning pharmacovigilance with environmental protection. In: Rahman SZ, Shahid M, Gupta V (eds.) An Introduction to Environmental Pharmacology. Ibn Sina Academy, Aligarh, India, pp. 21–34. [cited 2009 June 12]. Available from: http://www.epa.gov/nerlesd1/bios/daughton/IntroEnvironPharmacol-Chapter1-2008.pdf

D.U.M.P. (1997) Report on the Buckinghamshire D.U.M.P. (Dispose of Unwanted Medicines and Pills) Campaign October 1997. Buckinghamshire Health Authority, Aylesbury, Bucks, United Kingdom

ECON (2002) Kassasjon av legemidler. [Dispose of drugs]. ECON-rapport nr. 41/02. Prosjekt nr. 36520. 14. May 2002. ISBN 82-7645-525-5. [cited 2008 Oct 7]. Available from: http://www.econ.no/stream_file.asp?iEntityId=1225

Ekedahl A (2003) Unused drugs returned to pharmacies – a few patients return a large proportion of unused drugs. J Soc Adm Pharm 20, 257–258

Ekedahl A (2006) Reasons why medicines are returned to Swedish pharmacies unused. Pharm World Sci 28, 352–358

Ekedahl A, Wergeman L, Rydberg T (2003) Unused drugs in Sweden measured by returns to pharmacies. J Soc Adm Pharm 20, 26–31

Essential Services: Waste Management. [cited 2008 Oct 1]. Available from: http://www.psnc.org.uk/pages/essential_services_waste_management.html

Garey KW, Johle ML, Behrman K, Neuhauser MM (2004) Economic consequences of unused medications in Houston, Texas. Ann Pharmacother 38, 1165–1168

Gehler Mariacher G, Rota M, Hersberger KE (1998) Rücklauf ungenutzter Medikamente in Apotheken [Return of unused drugs to pharmacies]. Schweiz Rundsch Med Prax 87, 1441–1443

Götz K, Keil F (2007) Medikamentenentsorgung in privaten Haushalten: Ein Faktor bei der Gewässerbelastung mit Arzneimittelwirkstoffen? [Drug disposal in private households: Does

the disposal of pharmaceuticals via domestic sanitary devices contribute to water contamination?] USWF – Z Umweltchem Ökotox 19, 180–188. doi:10.1065/uwsf2007.07.201
Grainger-Rousseau T-J, Fielding DW, Smith MA, Daws D, Desrosiers D (1999) What's left in the medicine cabinet? The BC EnviRx Project. Poster No. 296. International Congress on Clinical Pharmacy, Orlando, FL April, 1999
Grant P (2001) Return of waste medicines to a community pharmacy. Prescriber 12, 29–38
Hawksworth GM, Wright DJ, Chrystyn H (1996) A detailed analysis of the day to day unwanted medicinal products returned to community pharmacies for disposal. J Soc Adm Pharm 13, 215–222
Heeke A, Günther J (1993) Arzneimittel im Müll. Eine studie der AOK Essen über nicht verbrauchte Arzneimittel. Deutsche Apotheker Zeitung 133, 4331–4337
Hepburn T, et al. (1997) Survey of unwanted medicines returned to pharmacies. Ayrshire & Arran Primary Care Drug and Therapeutics Committee. Ayrshire and Arran Health Board. Report January 1997
Herring ME, Shah SK, Shah SK, Gupta AK (2008) Current regulations and modest proposals regarding disposal of unused opioids and other controlled substances. J Am Osteopath Assoc 108, 338–343
Illinois-Indiana Sea Grant. Habitats and Ecosystems [homepage on the Internet]. Disposal of Unwanted Medicines: A Resource for Action in Your Community. Introduction. [cited 2008 Aug 27]. Available from: http://www.iisgcp.org/unwantedmeds/index.htm http://www.iisgcp.org/unwantedmeds/updatedToolKitMaterials/1.0Introduction.pdf
Isacson D, Olofsson C (1999) Drugs up in smoke: a study of caseated drugs in Sweden. Pharm World Sci 21, 96–99
Jones I, Britten N (1998) Why do some patients not cash their prescriptions. Br J Gen Pract 48, 903–905
Jonsson J (2000) Bortkastade pengar – en studie av kasserade läkemedel. [Wasted money – a studie of drugs disposed of] Apoteksgrupp Norrbotten, Norrbottens läkemedelskommitté 2000-04-16
Kallaos J, Wheeler K, Wong C, Zahller M (2007) Pharmaceuticals in wastewater streams: Disposal practices and policy options in Santa Barbara. [cited 2008 Aug 27]. Available from: http://www.bren.ucsb.edu/research/documents/Phar maceuticalsFinalReport.pdf
Kolar J, Chybova L, Holecko D (2001) [Unused drugs returned to pharmacies. I]. Ceska Slov Farm 50, 181–187
Kuspis DA, Krenzelok EP (1996) What happens to expired medications? A survey of community medication disposal. Vet Hum Toxicol 38, 48–49
Langley C, Marriott J, Mackridge A, Daniszewski R (2005) An analysis of returned medicines in primary care. Pharm World Sci 27, 296–299
Larsson DGJ, De Pedro C, Paxéus N (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Haz Mat 148, 751–755
Linton A (2003) Why Waste? Campaign Review of Drug Wastage in Antrim/Ballymena Locality. Report March 2003, Northern Health and Social Services Board, Northern Ireland
Longmore RB, Sunderland VB, Sansom LN (1995) Analysis of a "Medidump" campaign in Australia. Int J Pharm Pract 3, 186–191
Lynch JC, McCullough T (2008) The Collection and Disposal of Waste Medications. US Pharm [serial on the Internet] 33, HS-20–HS-24. [cited 2008 Aug 27]. Available from: http://www.uspharmacist.com/index.asp?show=article&page=8_2302.htm
Lægemiddelstyrelsen (2003) Hamstring af lægemidler i det behovsafhængige tilskudssystem. [Hoarding of drugs within the need dependent public insurance system]. Lægemiddelstyrelsen, Denmark 1 Apr 2003
Lægemiddelstyrelsen/Danmarks Apotekerforening (2001) Returmedicin på apotekerne. [Medicine return at pharmacies]. København, Denmark November 2001
Macarthur D (2000) Any old drugs? Two schemes for the disposal of unwanted medicines in Europe. Pharm J [serial on the Internet] 264, 223–224. [cited 2008 Aug 27]. Available from: http://www.pharmj.com/editorial/20000205/articles/olddrugs.html

Mackridge AJ, Marriott JF (2006) Unused medicines in primary care: a postal questionnaire. Int J Pharm Pract 14(S1), A23–A24

Mackridge AJ, Marriott JF (2007) Returned medicines: waste or a wasted opportunity? J Public Health 29, 258–262

Marchiset-Ferlay N, Gerbaud L, Sauvant MP, et al. (2001) [Description of unused drugs collected in pharmacies in the Puy-de-Dome region in France]. Rev Epidemiol Sante Publique 49, 551–558

McGovern EM, Tennant S, Mackay M (2002) Audit of returned medicines to community pharmacy. Pharm World Sci 24, A11–A12.

Medications Return Program [homepage on the Internet]. [cited 2008 Oct 1]. Available from: http://www.medicationsreturn.ca/

Metzger JW (2004) Drugs in municipal landfills and landfill leachates. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. 2nd edition, Springer, Berlin, Heidelberg, New York, pp. 133–137

Nguyen A, Tzianetas R, Louie S (2002) Responsible drug disposal program in North Vancouver. CMAJ 166, 1252–1253

Paterson JM, Anderson GM (2002) "Trial" prescriptions to reduce drug wastage: Results from Canadian programs and a community demonstration project. Am J Manag Care 8, 151–158

Phillips M, Allanson H, Shamsuddin T (1995) A survey of medicines returned to community pharmacists for disposal. Report Lancashire FHSA July 1995

RUM (Returning Unwanted Medicine) [homepage on the Internet]. [cited 2008 Oct 1]. Available from: http://www.returnmed.com.au/

Seehusen DA, Edwards J (2006) Patient practices and beliefs concerning disposal of medications. J Am Board Fam Med [serial on the Internet] 19, 542-547. [cited 2008 Aug 27]. Available from: http://www.jabfm.org/cgi/content/abstract/19/6/542

Sigre [homepage on the Internet]. [cited 2008 Oct 1]. Available from: http://www.sigre.es/farmacias_en_SIGRE.asp

Socialstyrelsen (2004) [Swedish National Board of Health and Welfare] Kasserade läkemedel. Förslag på åtgärder för att minska mängden överblivna läkemedel. [Discarded drugs. Suggested measures for reducing the amount of leftover drugs]. [cited 2008 Oct 30]. Available from: http://www.socialstyrelsen.se/Publicerat/2004/8474/2004-103-12.htm

Sullivan MJ, George CF (1996) Medicine taking in Southampton: a second look. Br J Clin Pharmacol 42, 567–571

Thormodsen M, Fonneløp H, Rytter E, Tørisen HM (1997a) Medisinretur som kvalitetsindikator for farmakoterapien – hva blir til overs? [Returned medicines as quality indicator for pharmacotherapy – what is left?]. Tidsskr Nor Laegeforen [serial on the Internet] 117, 3517–3520. [cited 2008 Oct 10]. Available from: http://ww2.tidsskriftet.no/tsweb/199724/art10.html

Thormodsen M, Fonneløp H, Rytter E, Tørisen HM (1997b) "Brukes etter avtale med legen" – årsaker til at pasienten får medisin til overs. ["To be used as directed by your doctor" – reasons why patients end up with unused medication]. Tidsskr Nor Laegeforen [serial on the Internet] 117, 3521–3525. [cited 2008 Oct 10]. Available from: http://ww2.tidsskriftet.no/tsweb/199724/art11.html

Valormed [homepage on the Internet]. [cited 2008 Oct 1]. Available from: http://www.valormed.pt

Wold G, Hunskår S (1992) Bruk og kast av medikamenter i hjemmet. Erfaringer fra en kommunal innsamlingsaksjon. [Use and disposal of drugs at home. Experiences of a community campaign for drug collection]. Tidsskr Nor Laegeforen 112, 1605–1607

Woolf M, Scott D (1995) Residual Medicines. OPCS Omnibus Survey Publications, Report 4. HM Stationery Office, London

Zimmer A, Graeser U, Wakolbinger A, Kreuter J (1999) Hessische Apotheken entsorgen jährlich 6 Millionen. Pharmazeutische Zeitung (PZ) [serial on the Internet] 03/1999. [cited 2008 Oct 8]. Available from: http://www.pharmazeutische-zeitung.de/fileadmin/pza/1999-03/pharm4.htm and Zimmer A, Graeser U, Wakolbinger A, Kreuter J (1999) Altarzneimittelstudie:

Rücklauf von Altarzneimitteln in hessischen Apotheken. Pharmazeutische Zeitung (PZ) 144, 23–30. [cited 2008 Oct 8]. Available from: http://www.kfunigraz.ac.at/pharmazie/pharmtech/docs/zimmer_12.pdf

Zimmer A, Zimmer AK, Kreuter J (1992) Rücklauf von Alt-Arzneimitteln in Apotheken. Pharmazeutische Zeitung (PZ) 137, 20–29

Chapter 13
Forecast of Pharmaceutical Consumption in the Netherlands Using Demographic Projections

Monique van der Aa and Geertjan Kommer

13.1 Demographic Make-up of Population Influences Burden of Disease

One of the main factors likely to shape future developments in public health and health care services are demographic changes in the population. Demographic (population) projections are "what-if" scenarios that provide an estimate of future size and structure of the population. Such projections take into account both increases driven by growth of the population and structural changes in the population, such as an ageing population. All other things being equal, the consequence of a larger population is an increase in the number of people requiring health care, while that of population ageing is an increased incidence of illnesses associated with older patients. It has been predicted that ageing and growth of the Dutch population will result in an increase in the number of persons with a chronic disease in the next 20 years, with the largest increase expected in the number of patients with diabetes and osteoporosis (Blokstra et al. 2007). The study of Hollander et al. (2007) on the demographic developments expected in the Netherlands in the period up to 2025 demonstrates that the biggest rises in prevalence can be expected in illnesses associated with advancing age, such as heart failure (40% population ageing-driven increase), dementia (38%) and stroke (37%). Conversely, the disorders that mainly affect younger people, such as asthma and mental disabilities, become proportionally less important.

In this chapter, we study the effects of growth and ageing of the population on the consumption of pharmaceuticals in the Netherlands. Demographic projections based on current (2007) age-specific consumption of pharmaceuticals combined with estimates of the size of different age classes in the future Dutch population were used to forecast future (2020) consumption of pharmaceuticals.

M. van der Aa (✉)
RIVM National Institute for Public Health and the Environment, 3720 BA Bilthoven, The Netherlands
e-mail: Monique.van.der.Aa@rivm.nl

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_13,

13.2 Pharmaceutical Consumption in the Netherlands in 2007

Data on the human consumption rates of prescribed pharmaceuticals were provided by the Foundation for Pharmaceutical Statistics in the Netherlands (Stichting Farmaceutische Kengetallen, SFK). SFK directly gathers its data from a consortium of pharmacies that currently comprise 1,760 (90%) of the 1,940 community pharmacies in the Netherlands (SFK 2008). To correct for this under-representation, SFK data were multiplied by a factor 10/9, assuming that these 1,760 pharmacies are representative of the Netherlands. The SFK consumption rates are for pharmaceuticals that are sold by public pharmacies and do not include the consumption of these pharmaceuticals in hospitals. According to McArdell (2009), the consumption of prescribed pharmaceuticals in Swiss hospitals is relatively small: 9% of the total consumption of a selection of 20 prescribed pharmaceuticals. Pharmaceuticals that are solely used in hospitals, such as X-ray contrast media, as well as pharmaceuticals that can be purchased at drug stores without a medical doctor's prescription (mostly analgesics) are also not included in the data. McArdell (2009) estimated that the consumption of analgesics in Switzerland sold by pharmacies is approximately 64% of the total consumption. In comparison, adaptation of the results of an American telephone survey on medication use by Kaufman et al. (2002) to the Dutch situation resulted in the estimate that 25–30% of the total consumption of ibuprofen and paracetamol is sold by pharmacies. Pharmaceuticals that are used for veterinary applications are also not included.

Thirty three pharmaceuticals, belonging to ten therapeutic groups, were selected as the basis for predicting future consumption using the following selection criteria:

- The pharmaceuticals are considered to be priority substances by the Dutch drinking water companies (Mons 2004, Van den Berg et al. 2007). Selection is based primarily on their occurrence in the water system and their resistance to treatment. These pharmaceuticals are erythromycin, sulfamethoxazole, metoprolol, sotalol, carbamazepin and acetyl salicylic acid.
- The pharmaceuticals are considered to be priority substances by the Global Water Research Coalition (GWRC 2008, de Voogt et al. 2009). Selection is based on the criteria regulation, consumption, physicochemical properties (such as polarity, chemical reactivity, degradation), toxicity, occurrence in surface waters, groundwater and drinking water, persistence and resistance to treatment.
- The pharmaceuticals belong to the top 50 of prescribed pharmaceuticals with the highest consumption rates in 2007 in the Netherlands, and are also excreted in the urine unchanged at a level of >50% (Van der Aa et al. 2008). Examples of such pharmaceutical are sulfamethoxazole, atenolol, irbesartan, valsartan, gabapentin and levetiracetam/keppra.

In 2007, the total consumption of prescribed pharmaceuticals in the Netherlands amounted to approximately 1,273 metric tons or 78 g per capita (gases, solvents, inorganic salts, auxiliary matter, proteins, vitamins, amino acids and vegetable extracts were excluded). The 33 pharmaceuticals selected for study constitute 555

metric tons (43%) of this total consumption (Table 13.1), with anti-diabetic drugs and analgesics accounting for more than half of this 555 metric tons.

Table 13.1 Forecast of the consumption of 33 selected pharmaceuticals, based on projections of the Dutch population between 2007 and 2020

Pharmaceutical group	Consumption 2007 (kg)	Consumption 2020 (kg)	Total growth (%)	Annual growth (%)
Heart and cardiovascular disease[a]	70,614	87,417	24	1.7
Gout medicines[b]	4,430	5,544	25	1.7
Anti-diabetic drugs[c]	230,211	284,559	24	1.6
Chemotherapy/ anticancer[d]	19	23	19	1.4
Ulcer treatment[e]	7,827	9,239	18	1.3
Analgesics[f]	185,734	218,877	18	1.3
Tranquilizer/ antidepressant[g]	666	747	12	0.9
Anti-epileptics[h]	21,674	23,890	10	0.8
Antibiotics[i]	33,753	36,719	9	0.6
Estrogens[j]	17	16	−3	−0.2
Total	554,946	667,030	20	1.4

[a]Irbesartan, valsartan (angiotensin II receptor antagonists), atenolol, metoprolol, sotalol (three beta blockers), chlorothiazide, furosemide (diuretic), bezafibrate, clofibric acid, gemfibrozil (all lipid regulators)
[b]Allopurinol
[c]Metformin
[d]Cyclophosphamide
[e]Ranitidine
[f]Acetyl salicylic acid, codeine, diclofenac, ibuprofen, naproxen, paracetamol (=acetaminophen)
[g]Diazepam, fluoxetine
[h]Carbamazepine, levetiracetam/keppra
[i]Amoxycillin, ciprofloxacin, clarithromycin, erythromycin, ofloxacin, sulfamethoxazole, trimethoprim
[j]Ethinylestradiol

13.3 Forecast of Pharmaceutical Consumption up to 2020 Based on Demographic Projections

Between 2007 and 2020, the Dutch general population is expected to increase from approximately 16.4 to 16.7 million people, which comes to a total increase of 2.4% or an average annual increase of 0.2% in this period. The largest increase will occur in the number of elderly, with an expected annual increase in individuals aged 65–74 years of 3.0% and a total increase of 47% in this period (Fig. 13.1). According to Hollander et al. (2007), the percentage of the Dutch population aged 65+ years will increase from its present level of about 14% to a peak of about 24% in 2040. This rise is mainly due to the “baby boom” after the Second World War. Between 2007

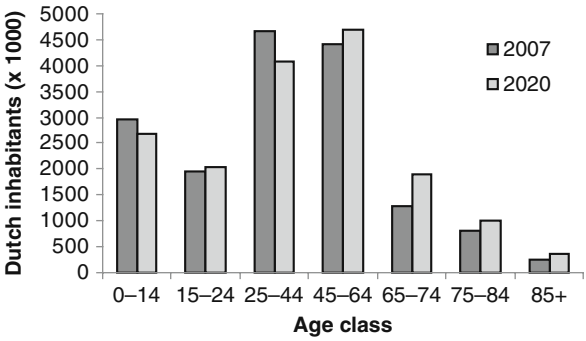


Fig. 13.1 Demographic trends in the Netherlands according to age class (Source: statline)

and 2020 a decrease is expected in individuals aged 0–14 years and 25–44 years.

The forecast of future consumption is based on the consumption attributable to different age classes of both sexes in 2007, combined with the Statistics Netherlands' population prognosis for the period 2007–2020, assuming a fixed consumption rate – that of 2007. The results are shown in Table 13.1 and demonstrate that demographic developments alone will push consumption up from about 555 metric tons in 2007 to 667 by 2020. Most of this demographic driven growth will result from population ageing (Fig. 13.1). The consumption of gout (metabolic arthritis) medicines, pharmaceuticals for cardiovascular diseases and anti-diabetic drugs are expected to increase the most: 24–25% between 2007 and 2020, which is an average annual increase of 1.6–1.7%. Anti-diabetic drugs, together with analgesics, also show the greatest consumption in terms of kilograms, both in 2007 and in 2020. Average increases are expected in the consumption of analgesics and pharmaceuticals for ulcer treatment and anticancer/chemotherapy: an 18–19% increase between 2007 and 2020, which is an annual average increase of 1.2–1.4%. In contrast, the consumption of ethinyl-estradiol, an estrogen and active compound in anti-contraceptives, is expected to decrease. This is related to the decreasing number of women in the age class 25–44 (Fig. 13.1). Women in the age classes 15–24 and 25–44 are the groups where consumption of ethinyl-estradiol predominantly takes place.

Uncertainties in the demographic projections tend to grow with increasing length of the projection period. By 2015, the Dutch population is expected to reach 16.6 million people, with a 67% probability that it will be between 16.2 and 16.9 million. For the 2050 projection, this range increases. Although it is likely that the Dutch population will increase in the coming decennia, it cannot be excluded that the population may begin to decrease before 2015 (Verweij et al. 2007). The extrapolation of these uncertainties in the demographic projections leads to the conclusion that the predicted total consumption of 667 metric tons in 2020 with a probability of 67% will be between 687 (+3%) and 640 metric tons (–4%).

13.4 European Perspective of the Dutch Forecasts

The consumption of pharmaceuticals in the Netherlands differs from that of other European countries. These differences have been quantified for seven pharmaceuticals in Fig. 13.2. These quantities underestimate the total usage, since pharmaceuticals which can be purchased without a pharmacy prescription (e.g. use in hospitals) and those procured illegally are not included. Figure 13.2 shows that the per-capita consumption rates of these seven drugs in the Netherlands are relatively low compared to those of the other countries, with the exception of diazepam. This result is in agreement with data published by the SFK (2008) showing that medicine consumption is 12–60% higher in those countries neighbouring the Netherlands.

Another difference between countries concerns differences in population prognosis. Similar to the trend forecast for total EU-27 population, the Dutch population is projected to grow until around 2035 – from 16.4 million in 2007 to a maximum of 17.3 million in 2036 – and then to decline – to 16.6 million in 2060. With an expected population growth of 1.5% between 2007 and 2060, the Netherlands belongs to the group of countries with the smallest predicted difference in population size between these years (Fig. 13.3).

The projection of Eurostat (2008) is that the total EU-27 population will grow by more than 15 million persons – from 495.1 million in 2007 to a maximum of 520.7 million in 2035. It will then gradually decline to 505.7 million in 2060, which is about 10 million (or 2.1%) more persons than in 2007. Not all countries will

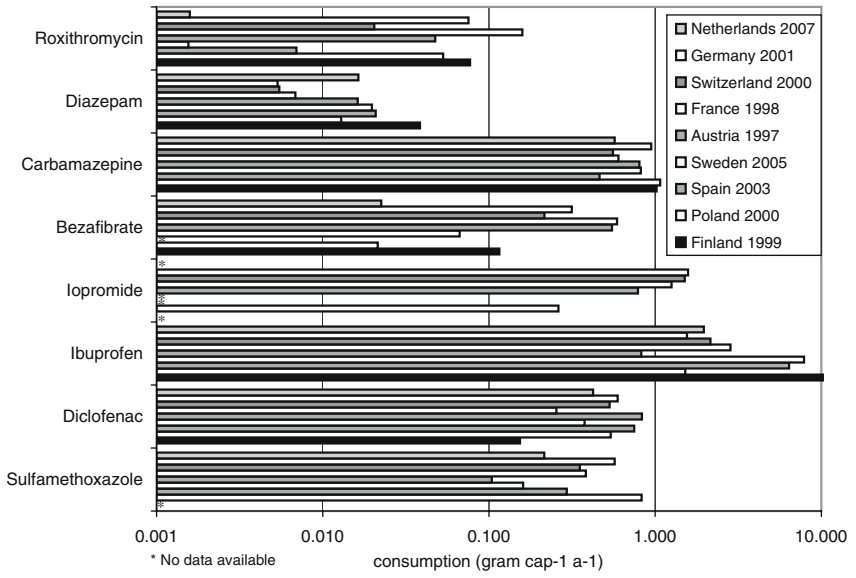


Fig. 13.2 Comparison of annual prescribed consumption rates of pharmaceuticals investigated in the POSEIDON project (Alder et al. 2006) with data from the Netherlands (2007)

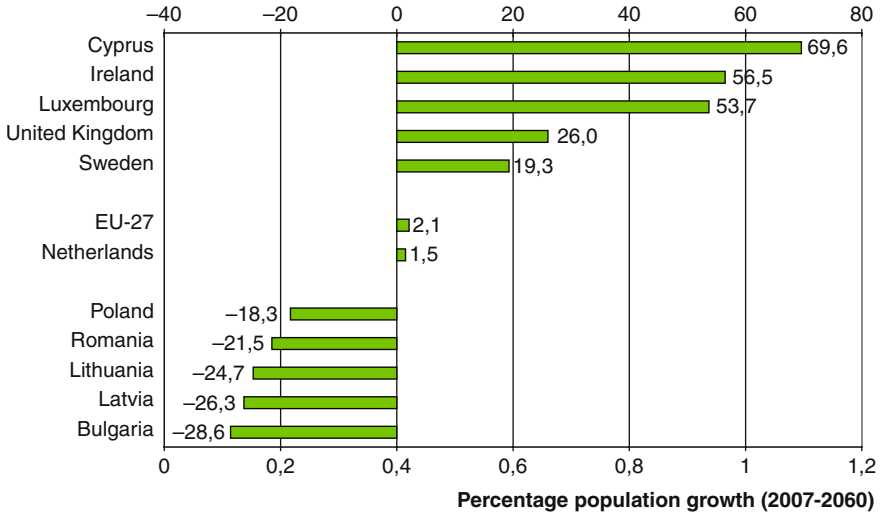


Fig. 13.3 EU-27 countries with the highest percentage population growth and the highest percentage population decline between 2007 and 2060 (Eurostat 2008). Taken from: Harbers et al. (2008)

have a larger population in 2060; in fact, about half of the EU-27 Member States will actually have a smaller population in 2060 than in 2007 (Table 13.2), with the declines expected to be largest in Bulgaria, Latvia, Lithuania, Romania and Poland (Fig. 13.3). The countries predicted to have the largest relative growth between 2007 and 2060 are Cyprus, Ireland, Luxembourg, United Kingdom and Sweden. The demographic changes between 2007 and 2060 will have a moderate impact on the proportional representation of each Member State in the total EU-27 population.

Table 13.2 Total population in 2007 and projected population in 2060 (in millions) in EU-27 countries (Eurostat 2008). Taken from: Harbers et al. (2008)

Country	2007	2060	Country	2007	2060
EU-27	495.1	505.7	Austria	8.3	9.0
United Kingdom	60.9	76.7	Hungary	10.1	8.7
France	63.4	71.8	Ireland	4.3	6.8
Germany	82.3	70.8	Denmark	5.4	5.9
Italy	59.1	59.4	Bulgaria	7.7	5.5
Spain	44.5	51.9	Finland	5.3	5.4
Poland	38.1	31.1	Slovakia	5.4	4.5
Romania	21.6	16.9	Lithuania	3.4	2.5
Netherlands	16.4	16.6	Slovenia	2.0	1.8
Belgium	10.6	12.3	Latvia	2.3	1.7
Portugal	10.6	11.3	Cyprus	0.8	1.3
Greece	11.2	11.1	Estonia	1.3	1.1
Sweden	9.1	10.9	Luxembourg	0.5	0.7
Czech Republic	10.3	9.5	Malta	0.4	0.4

Germany had the largest population in 2007, but the United Kingdom is predicted to be the most populous country in the EU in 2060. This change is the result of a steadily increasing population in the United Kingdom, whereas the decrease in the German population that started in 2003 will continue (Eurostat 2008).

13.5 Discussion

In the Netherlands, one of the European countries with the smallest difference between current and projected future population size, the consumption of 33 selected pharmaceuticals, all assessed to be important based on pre-selected criteria, is expected to increase by 20% between 2007 and 2020 based on demographic projections. A critical assumption when using demographic projections for quantifying future pharmaceutical consumption is that this future consumption will be influenced only by changes in the size and structure of that population under study. In reality, however, consumption is subject to many other factors, including epidemiological changes and developments in the provision of public health and medical technology. Historical analyses show that such factors have in the past exerted more influence on the cost of health care provision than demographic developments (Hollander et al. 2007). At the same time, changes in health care consumption are difficult to predict. Much depends not only on the technologies that come onto the market but also on developments/changes in what society views as an appropriate level of health care. Nevertheless, these demographic based growth rates reveal a quantified trend for future consumption and potential emissions of pharmaceuticals to the water system. Policy-makers can use this information to anticipate and develop appropriate emission reduction strategies.

References

Aa NGFM van der, Kommer GJ de, Groot GM, Versteegh JFM (2007) Pharmaceuticals in sources for drinking water – monitoring, future consumption and policy measures. RIVM report 609715002, 2008 (in Dutch, with English abstract), Bilthoven, The Netherlands

Alder AC, Bruchet A, Carballa M, Clara M, Joss A, Löffler D, McArdell CS, Miksch K, Omil F, Tuhkanen T, Ternes TA (2006) Consumption and occurrence. In: Ternes, TA, Joss A (eds.) Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management. IWA Publishing, London, pp. 15–54

Berg G vanden, de Rijk S, Abrahamse A, Puijker L (2007) Bedreigende stoffen voor drinkwater uit de Maas. KWR 07.055. KIWA, Nieuwegein (in Dutch)

Blokstra A, Verschuren WMM, Baan CA, Boshuizen HC, Feenstra TL, Hoogenveen RT, Picavet HSJ, Smit HA, Wijga AH (ed.) (2007) Impact of the ageing population on burden of disease - projections of chronic disease prevalence for 2005-2025. RIVM rapport 260401004/2007 (in Dutch, with English abstract), Bilthoven, The Netherlands

Eurostat (2008) Statistical Database of the European Union. http://epp.eurostat.ec.europa.eu/

GWRC (2008) Development of an International Priority List of Pharmaceuticals Relevant for the Water Cycle. Prepared by Kiwa Water Research, CIRSEE and TZW, Global Water Research Coalition, London, UK

Harbers MM, Wilk EA van der, Kramers PGN, Kuunders MMAP, Verschuuren M, Eliyahu H, Achterberg PW (2008) Dare to Compare! Benchmarking Dutch health with the European Community Health Indicators (ECHI). RIVM report number 270051011. Bohn Stafleu Van Loghum, Houten

Hollander AEM de, Hoeymans N, Melse JM, Oers JAM van, Polder JJ (eds.) (2007) Care for health – The 2006 Dutch Public Health Status and Forecasts Report. RIVM report number 270061003 (ISBN-10 90-6960-148-6; ISBN-13: 978-90-6960-148-6 NUR 860), Bilthoven, The Netherlands

Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA (2002) Recent patterns of medication use in the ambulatory adult population of the United States – The slone survey. JAMA 287(3), 337–344

McArdell (2009) Presentation at Xenowac conference Cyprus, 11–13 March 2009

Mons M (2004) Summary information pharmaceuticals. BTO 2004.004. Kiwa, Nieuwegein (in Dutch)

SFK (2008) Facts and Figures. Foundation for Pharmaceutical Statistics. The Hague, The Netherlands

Statline, http://statline.cbs.nl

Verweij A, Bongers SW, Beer J de (2007) Onzekerheden prognoses bevolking. In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, www.nationaalkompas.nl, Bevolking, 21 September 2007 (in Dutch). Bilthoven, The Netherlands

Voogt P de, Janex-Habibi ML, Sacher F, Puijker L, Mons M (2009) Development of a common priority list of pharmaceuticals relevant for the water cycle. Water Sci Technol –WST 59(1), 39–46

Part IV
Emission Management

Chapter 14
Point Sources of Human Pharmaceuticals into the Aquatic Environment

Kevin V. Thomas and Katherine H. Langford

14.1 Sources of Human Pharmaceuticals

It is generally accepted that treated sewage effluent discharges are the principal source of pharmaceutically active compounds and their metabolites from humans into the aquatic environment (Daughton and Ternes 2000, Heberer 2002). As has been discussed in other chapters of this book in order for the sustainable use of pharmaceuticals to become a reality there is a need to understand the complete life cycle of a pharmaceutical compound including the various pathways by which it can enter the aquatic environment. Sewage treatment works (STWs) serving even the smallest municipality can receive wastewater from a number of sources that may be sources of human pharmaceuticals into the aquatic environment (Fig. 14.1). For the purpose of this chapter three main routes by which human pharmaceuticals can enter the environment are considered: in effluents discharged by manufacturing, from the disposal of unused medicines and via the excretion products of patients undergoing treatment. For example it is not uncommon for wastewater treatment works to receive effluent from homes, offices, factories, hospitals and pharmaceutical manufacturing plants. Pharmaceuticals in waste from homes may be broken down to that which has been used and passed as metabolites or unchanged parent pharmaceutical or which has been disposed by flushing down the sink/toilet or disposed of as household waste (Bound and Voulvoulis 2005). Mass flow data from the UK suggests that disposal of unused drugs via the sink/toilet is low when compared to the amounts used and disposed of through other routes such as disposal to household waste (Bound et al. 2006, see however data from Götz and Deffner, Chap. 10, this book). In this chapter we consider the inputs from point sources such as hospitals and manufacturing facilities using the data currently available. In order to study the respective loadings from these sources, published data have been compiled on the occurrence and more importantly the mass loadings from hospitals and production facilities.

K.V. Thomas (✉)
Norwegian Institute for Water Research (NIVA), NO-0349 Oslo, Norway
e-mail: kevin.thomas@niva.no

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_14,

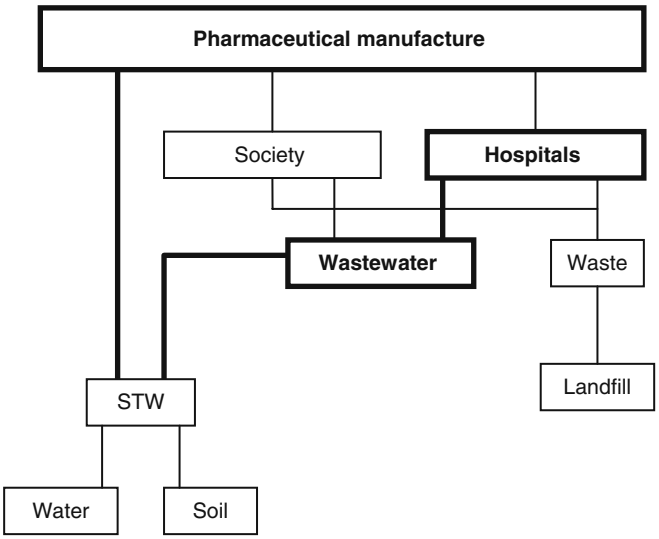


Fig. 14.1 Pathway of human pharmaceuticals from point sources into the environment

14.2 Hospital Effluents

Hospital effluents have received the greatest attention as a point source of human pharmaceuticals into the environment. Kümmerer (2001) reviewed the emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals and reported early studies of the occurrence of human pharmaceuticals. Kümmerer and Henninger (2003) reports that, in Germany during 1999, hospitals were responsible for 26% (105 t) of the country's antibiotic consumption and estimated that 86 t of antibiotic agents were released into the aquatic environment from hospitals. On a regional level antibiotic emission may however be lower (Schuster et al. 2008). As for other compounds hospitals appear to be a minor source (Heberer and Feldmann 2005, Schuster et al. 2008). Measured data show that hospital effluents can contain a number of different pharmaceuticals, including antibiotics, analgesics, anti-inflammatories, lipid regulators and antitumor amongst others (Table 14.1). The fluoroquinolone antibiotic ciprofloxacin is the most studied pharmaceutical in hospital effluents with data available from numerous European, US and Asian hospital effluents. In all of the studies reported to date the annual hospital load of ciprofloxacin has been between 1.5 and 10.5 kg. In Oslo, Norway, the hospital load of ciprofloxacin has been estimated to be approximately 40% of the city's total load (Table 14.1; Thomas et al. 2007). The concentration of ciprofloxacin in hospital effluents is generally high with concentrations of up to 125 μg/l reported. For example Hartmann and co-workers (1998) reported concentrations of fluoroquinolone antibiotics, and specifically ciprofloxacin, at concentrations of between 2 and 83 μg/l in the effluent of a large Swiss hospital and even higher

Table 14.1 Overview of pharmaceutical concentrations in effluents from hospitals (for maximum loads of antibiotics see also Kümmerer and Henninger 2003)

Pharmaceutical	Location	Concentration (μg/l)		Annual discharge (kg)	References
		Min.	Max.		
Aminoantipyrin/4-Acetylaminoantipyrin	Berlin, Germany	57	77	11	Feldmann et al. (2008)
Ampicillin	5 in Taiwan		5,080		Lin and Tsai (2009)
Atenolol	Almera, Spain	3			Gomez et al. (2006)
Atenolol	Riks, Oslo, Norway	90			Langford and Thomas (2009)
Atenolol	Ullevål, Oslo, Norway	59.3			Langford and Thomas (2009)
Atorvastatin	Riks, Oslo, Norway	3			Langford and Thomas (2009)
Atorvastatin	Ullevål, Oslo, Norway	6.24			Langford and Thomas (2009)
ß-lactams	Germany	20	80		Kümmerer (2001)
Carbamazapine	Almera, Spain	0			Gomez et al. (2006)
Carbamazapine	RIKS, Oslo, Norway	11,646			Langford and Thomas (2009)
Carbamazapine	Ullevål, Oslo, Norway	2,401.6			Langford and Thomas (2009)
Carboplatin	Vienna, Austria	40			Lenz et al. (2007)
Carisoprodol	RIKS, Oslo, Norway	5.2			Langford and Thomas (2009)
Carisoprodol	Ullevål, Oslo, Norway	9.6			Langford and Thomas (2009)
Cefuroxime	RIKS, Oslo, Norway		<125		Thomas et al. (2007)
Cefuroxime	Ullevål, Oslo, Norway	<125	<125		Thomas et al. (2007)
Chloramphenicol	Würzburg, Germany				Ohlsen et al. (2003)
Chlortetracycline	5 in Taiwan		2.8		Lin and Tsai (2009)
Ciprofloxacin	5 in Germany	0.7	125.0		Hartmann et al. (1999)

Table 14.1 (continued)

Pharmaceutical	Location	Concentration (μg/l)		Annual discharge (kg)	References
		Min.	Max.		
Ciprofloxacin	Hanoi, Vietnam	1.1	44.0	5.7	Duong et al. (2008)
Ciprofloxacin	Kalmar, Sweden	3.6	101.0		Jarnheimer et al. (2004), Lindberg et al. (2004)
Ciprofloxacin	RIKS, Oslo, Norway	0.002	39.8	1.46	Thomas et al. (2007)
Ciprofloxacin	Switzerland	3.0	87.0		Alder et al. (2004)
Ciprofloxacin	Ullevål, Oslo, Norway	<0.04	54.0	10.5	Thomas et al. (2007)
Ciprofloxacin	Würzburg, Germany	2.0	51		Ohlsen et al. (2003)
Ciprofloxacin	Zurich, Switzerland	21.0		4.6	Hartmann et al. (1999)
Claithromycin	Würzburg, Germany		2		Ohlsen et al. (2003)
Codeine	Almera, Spain	1			Gomez et al. (2006)
Cyclophosphamide	RIKS, Oslo, Norway		<2		Thomas et al. (2007)
Cyclophosphamide	Ullevål, Oslo, Norway	<2	21		Thomas et al. (2007)
Diclofenac	Almera, Spain	1			Gomez et al. (2006)
Diclofenac	RIKS, Oslo, Norway	0.16	14,934	0.16	Thomas et al. (2007)
Diclofenac	Ullevål, Oslo, Norway	238	1,629	0.3	Thomas et al. (2007)
Diclofenac	6 in Taiwan		70,000		Lin and Tsai (2009)
Doxorubicin	Vienna, Austria	0	1		Mahnik et al. (2007)
Erythromycin	Almera, Spain	0			Gomez et al. (2006)
Erythromycin	Würzburg, Germany		27		Ohlsen et al. (2003)
Erythromycin-H_2O	Würzburg, Germany		83		Ohlsen et al. (2003)
Erythromycin-H_2O	6 in Taiwan		6,110		Lin and Tsai (2009)
Furosemide	RIKS, Oslo, Norway		196		Langford and Thomas (2009)

Table 14.1 (continued)

Pharmaceutical	Location	Concentration (μg/l)		Annual discharge (kg)	References
		Min.	Max.		
Furosemide	Ullevål, Oslo, Norway		392		Langford and Thomas (2009)
Gemfibrozil	6 in Taiwan		1,110		Lin and Tsai (2009)
Gentamicin	Würzburg, Germany		5		Ohlsen et al. (2003)
Ibuprofen	Almera, Spain	20			Gomez et al. (2006)
Ibuprofen	RIKS, Oslo, Norway	0.13	8,957	0.13	Thomas et al. (2007)
Ibuprofen	Ullevål, Oslo, Norway	69	987	0.2	Thomas et al. (2007)
Ibuprofen	6 in Taiwan		300		Lin and Tsai (2009)
Ifosfamide	RIKS, Oslo, Norway		291		Thomas et al. (2007)
Ifosfamide	Ullevål, Oslo, Norway	<2	338		Thomas et al. (2007)
Indomethacin	RIKS, Oslo, Norway				Langford and Thomas (2009)
Indomethacin	Ullevål, Oslo, Norway				Langford and Thomas (2009)
Ketoprofen	RIKS, Oslo, Norway	180			Langford and Thomas (2009)
Ketoprofen	Ullevål, Oslo, Norway	227.1			Langford and Thomas (2009)
Ketoprofen	3 in Taiwan		231		Lin and Tsai (2009)
Ketorolac	Almera, Spain	4			Gomez et al. (2006)
Mefenamic acid	RIKS, Oslo, Norway	2			Langford and Thomas (2009)
Mefenamic acid	Ullevål, Oslo, Norway	84			Langford and Thomas (2009)
Metoprolol	RIKS, Oslo, Norway	0.35	25,097	0.35	Thomas et al. (2007)
Metoprolol	Ullevål, Oslo, Norway	419	2,232	0.4	Thomas et al. (2007)
Metronidazole	Almera, Spain	6			Gomez et al. (2006)

Table 14.1 (continued)

Pharmaceutical	Location	Concentration (μg/l)		Annual discharge (kg)	References
		Min.	Max.		
Naproxen	6 in Taiwan		1,010		Lin and Tsai (2009)
Norofloxacin	Hanoi, Vietnam	1	17	4.6	Duong et al. (2008)
Norofloxacin	Würzburg, Germany		44		Ohlsen et al. (2003)
Norofloxacin	Zurich, Switzerland	5		1.2	Alder et al. (2004)
Ofloxacin	Kalmar, Sweden	0			Jarnheimer et al. (2004), Lindberg et al. (2004)
Ofloxacin	Würzburg, Germany		31		Ohlsen et al. (2003)
Oxytetracycline	RIKS, Oslo, Norway		2,294		Thomas et al. (2007)
Oxytetracycline	Ullevål, Oslo, Norway	<12	3,743		Thomas et al. (2007)
Oxytetracycline	3 in Taiwan		14		Lin and Tsai (2009)
Paracetamol	RIKS, Oslo, Norway	20.51	1,368,474	20.51	Thomas et al. (2007)
Paracetamol	Ullevål, Oslo, Norway	13,874	177,674	20.4	Thomas et al. (2007)
Paracetamol	6 in Taiwan		186,500		Lin and Tsai (2009)
Paroxetine	RIKS, Oslo, Norway	19			Langford and Thomas (2009)
Paroxetine	Ullevål, Oslo, Norway	12.9			Langford and Thomas (2009)
Phenazone	RIKS, Oslo, Norway	45			Langford and Thomas (2009)
Phenazone	Ullevål, Oslo, Norway	220			Langford and Thomas (2009)
Propranolol	Almera, Spain	1			Gomez et al. (2006)
Propranolol	RIKS, Oslo, Norway	38,182			Langford and Thomas (2009)
Propranolol	Ullevål, Oslo, Norway	15,396			Langford and Thomas (2009)

Table 14.1 (continued)

Pharmaceutical	Location	Concentration (μg/l)		Annual discharge (kg)	References
		Min.	Max.		
Propranolol	6 in Taiwan		225		Lin and Tsai (2009)
Ranitidine	Almera, Spain	1			Gomez et al. (2006)
Roxithromycin	Würzburg, Germany		1		Ohlsen et al. (2003)
Simvastatin	RIKS, Oslo, Norway	<1			Langford and Thomas (2009)
Simvastatin	Ullevål, Oslo, Norway	2.2			Langford and Thomas (2009)
Sulfadimidin	Würzburg, Germany				Ohlsen et al. (2003)
Sulfamethazine	Taiwan		2.8		Lin and Tsai (2009)
Sulfamethoxazole	RIKS, Oslo, Norway	0.11	4,107	0.11	Thomas et al. (2007)
Sulfamethoxazole	Ullevål, Oslo, Norway	<4	1,375	0.1	Thomas et al. (2007)
Sulfamethoxazole	6 in Taiwan		7,350		Lin and Tsai (2009)
Sulfamethoxazole	Würzburg, Germany		6		Ohlsen et al. (2003)
Sulfamethoxine	Taiwan		8.6		Lin and Tsai (2009)
Tetracycline	RIKS, Oslo, Norway	0.13	4,178	0.13	Thomas et al. (2007)
Tetracycline	Ullevål, Oslo, Norway	<15	1,537	0.1	Thomas et al. (2007)
Tetracycline	6 in Taiwan		455		Lin and Tsai (2009)
Trimethoprim	Almera, Spain	0			Gomez et al. (2006)
Trimethoprim	RIKS, Oslo, Norway	0.28	11,899	0.28	Thomas et al. (2007)
Trimethoprim	Ullevål, Oslo, Norway	50	14,993	0.8	Thomas et al. (2007)
Trimethoprim	Würzburg, Germany		6		Ohlsen et al. (2003)

(up to 125 μg/l) in five German hospitals (Hartmann et al. 1999). The antibiotics ciprofloxacin and ofloxacin were detected at much lower concentrations in effluent from a Swedish hospital; however this study showed that high concentrations can be found associated with sludge (Ohlsen et al. 2003). Adsorption to

sludge is indeed an important removal mechanism for fluoroquinolone antibiotics and plays a key role in assessing environmental loading since partition to sludge between the point of entry into the sewage network and wastewater treatment works. Ciprofloxacin has been responsible for bacterial DNA damage in German hospital effluents (Hartmann et al. 1999) and bacterial (*E. coli*) resistance (along with norfloxacin) in Vietnamese hospital effluents (Duong et al. 2008). This later study contradicted the work of Reinthaler and co-workers (Reinthaler et al. 2003) whom reported that ciprofloxacin and norfloxacin were 100% effective against *E. coli* in the influent and sludge of two Swedish STWs. The occurrence of antibiotics in hospital sewage effluent does raise fears of antimicrobial resistance which is an important threat to public health. It is currently believed that bacteria remain unaffected when exposed to antibiotics under standard test conditions such as those recommended by the OECD (Kümmerer 2004a,b; Al-Ahmad et al. 1999). Many studies have also shown that the antibiotic concentrations in hospital effluent are often below concentrations that can lead to resistance (Ohlsen et al. 2003), although in general it is accepted that the significance of antibiotics in the environment is not clear (Kümmerer 2004a,b). Other antibiotics that have been detected in hospital effluents include erythromycin, doxorubicin, gentamicin, norofloxacin, ofloxacin, oxytetracyclin, roxrythromycin, sulfadimidin, sulfdamethoxazole, tetracycline and trimethoprim (Table 14.1). Occurrence data for these antibiotics suggest that they are present in hospital effluents at μg/l concentrations depending on the amount prescribed by the hospital which equates to loadings of a up to a few kg/year, where data are available (Fig. 14.2). This compares with much greater concentrations of analgesics such as paracetamol, ibuprofen and diclofenac. For example, a study from Oslo, Norway suggests hospital effluents can contain high concentrations of paracetamol ($\leq$1,368 μg/l) which equates to an annual loading of around 20 kg (Thomas et al. 2007).

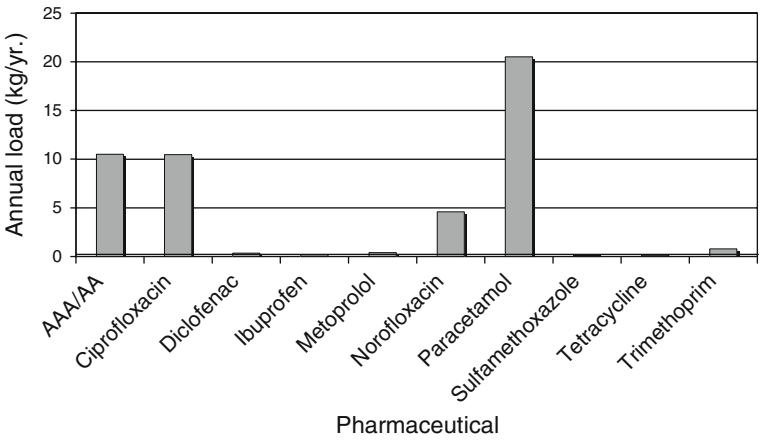


Fig. 14.2 Annual load of selected human pharmaceuticals from hospitals. Maximum published value used. AAA/AA=Aminoantipyrin and 4-Acetylaminoantipyrin

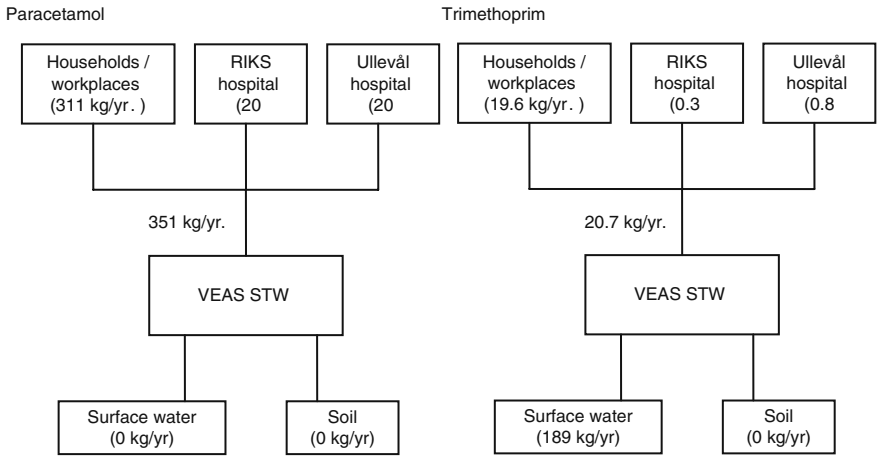


Fig. 14.3 Mass flow of paracetamol and trimethoprim within Oslo, Norway

A comparison of the pharmaceutical loading from hospitals with those from general domestic sources suggests that hospitals are not generally a significant source of pharmaceuticals to STWs. When the mass flow of selected pharmaceuticals from two Oslo city hospitals were compared with that of the rest of the city it was found that only ciprofloxacin and paracetamol contributed significantly to the general loading of the receiving STW, VEAS. Mass flow data showed that the hospital loadings were typically <2% of the STWs total loadings (Langford and Thomas 2009, Thomas et al. 2007) and is illustrated in Fig. 14.3. Modelling tools, such as the MOUSE model (Muthanna and Plosz 2008) can be used to model pharmaceutical mass flow data from hospitals and provide valuable data on the affect of management decisions within the hospital on pharmaceutical release. In light of the generally low comparative loads released from hospitals, modelling may be the most cost-affective approach when assessing pharmaceutical release from hospitals.

14.3 Manufacturing Sites

Published monitoring, or indeed occurrence data for effluents from manufacturing sites are few and far between. Recent data released by AstraZeneca for two manufacturing facilities in Sweden show that ng to μg/l concentrations of manufactured pharmaceuticals can occur in the final effluent even following extensive wastewater treatment with pH control, fungal and bacterial reactors, carbon adsorption, chemical precipitation and sand filtration stages (Boegård et al. 2008). The occurrence of many of the targeted pharmaceuticals was at similar concentrations to those found in wastewater effluents receiving mainly domestic waste (Fig. 14.4) (Thomas and Langford 2007). Toxicity testing of these effluents with both a 72 h *Selenastrum capricmutum* and a 14 day *Daphnia magna* life-cycle toxicity test showed no

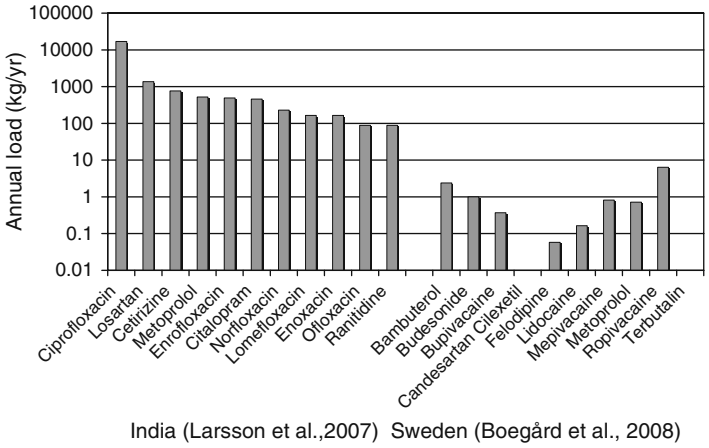


Fig. 14.4 Comparison of annual pharmaceutical loads from a manufacturing facility in India and Sweden

chronic toxicity in samples up to and including 10% (v/v). The effluent occurrence data were also used to derive predicted environmental concentrations (based upon 1,000 × dilution in the recipient) that were used for a simple risk assessment (PEC/PNEC) using published PNEC (www.FASS.se or lowest acute LC50/1000) and showed that the effluents entering from a well managed plant, such as the AstraZeneca Södertälje facility, contain residues of individual active pharmaceutical ingredients below those levels currently thought to cause environmental effects.

Recent reports from China (Li et al. 2008), Taiwan (Lin and Tsai 2009) and India (Larsson et al. 2007) though paint a different picture. Larsson et al. (2007) reported the occurrence of "extremely high levels of pharmaceuticals" in effluent from a wastewater treatment plant serving 90 bulk drug manufacturers in Patancheru, near Hyderabad, India. The Patancheru Enviro Tech Ltd. plant treats around 1,500 m^3 of effluent, primarily from around 90 bulk drug manufacturers. Following a screening analysis to see which compounds were present, eleven drugs were analysed further and found to be present at concentrations in excess of 100 μg/l and for certain compounds (i.e. ciprofloxacin) up to 31,000 μg/l. The majority of the pharmaceuticals detected at these high concentrations were fluoroquinolone antibiotics with proton-pump inhibitors such as cetirizine and ranitidine also present. The quantities of pharmaceuticals being released into the environment from this treatment facility are quite substantial and are orders of magnitude greater than what is typically released from a wastewater treatment works serving a typical city (Fig. 14.4). For example this WTW releases around 17 t of ciprofloxacin each year and 100 kg quantities of the other drugs analyzed. As pointed out by Larsson et al. (2007), these levels pose a real risk of acute effects to the receiving environment, whilst there is a clear potential for long-term chronic effects and antibiotic resistant bacteria. These high levels are not restricted to India with Li et al. (2008) reporting the occurrence of high concentrations of oxytetracycline (19,500 ± 2,900 μg/l) in the treated outflow effluent from a wastewater treatment works in Nebei Province. This

represents quantities even higher than those reported from India with nearly 100 t of oxytetracycline alone being discharged into the aquatic environment (Li et al. 2008). Analysis of waste streams from Taiwan suggests that production facilities in certain countries are releasing high quantities of active pharmaceutical compounds into the environment (Lin and Tsai 2009). In Taiwan for example high concentrations of sulfamethoxazole (1,340 μg/l) and ibuprofen (1,500 μg/l) were consistently measured in effluents from at least three different pharmaceutical production facilities.

These data contrast greatly with those released by AstraZeneca for their Södertälje facility where typically less than 1 kg of each active is released annually (Boegård et al. 2008). Few published pharmaceutical occurrence data are available for effluents from manufacturing plants but the studies presented above paint very different pictures (Fig. 14.4). It would appear from the very limited data that effluent from facilities managed by R&D pharma companies, such as AstraZeneca, release low levels of pharmaceuticals when compared to the mass production facilities in Hyderbalad, India, China or Taiwan. The few studies available make this a very general statement.

14.4 Conclusion

Point source data for hospitals and in particular manufacturing facilities are particularly scarce. Understanding the contribution of such activities to the overall environmental pharmaceutical load requires such data to be available. The few data available suggest that generally hospitals contribute between gram and low kg quantities of individual pharmaceuticals into the sewer network which are typically negligible when compared to the overall loading from general society (Fig. 14.5).

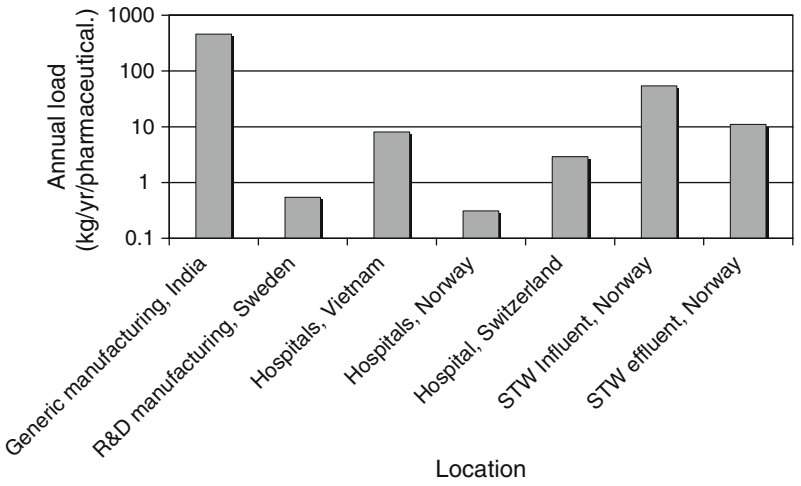


Fig. 14.5 Comparison of the median annual pharmaceutical loads from manufacturing facilities and hospitals

Data for manufacturing facilities are extremely scarce with four contrasting studies having been published. This work suggests certain generic manufacturers, such as those in Hyderbalad India, Taiwan and China, contribute significantly to the environmental loading of pharmaceuticals, whilst well managed R&D pharma-company facilities with advanced wastewater treatment in Europe and North America, such as AstraZeneca's in Sweden, contribute no more than the average hospital. In general, the severe lack of data for point-sources as a whole makes any comparison tentative. The few studies indicate a great variety of pharmaceutical input into the aquatic compartment. Thus, more relevant data are needed to assess the real impact of point-sources, such as hospitals and manufacturing sites, for the environment.

References

Al-Ahmad A, Daschner FD, Kümmerer K (1999) Biodegradability of cefotiam, ciprofloxacin, meropenem, penicillin G, and sulfametohoxazole and inhibition of wastewater bacteria. Arch Environ Con Tox 37, 158–163

Alder AC, McArdell CS, Golet EM, Kohler H-P, Molnar E (2004) Environmental exposure of antibiotics in wastewaters, sewage sludges and surface waters. In: Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. Springer, Berlin

Boegård C, Coombe V, Holm G, Taylor D (2008). The concentrations and potential environmental impact of pharmaceuticals in the effluent from a major Astrazeneca manufacturing facility. KNAPPE- Pharmaceutical Products in the Environment: Trends toward lowering occurrence and impact. Nimes, France

Bound JP, Kitsou K, Voulvoulis N (2006) Household disposal of pharmaceuticals and perception of risk to the environment. Environ Toxicol Pharmacol 21, 301–307

Bound JP, Voulvoulis N (2005) Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environ Health Perspect 113, 1705–1711

Daughton CG, Ternes TA (2000) Pharmaceuticals and personal care products in the environment: Agents of subtle change? Environ Health Perspect 107, 906–946

Duong HA, Pham NH, Nguyen HT, Hoang TT, Pham HV, Pham VC, Berg M, Giger W, Alder AC (2008) Occurrence, after and antibiotic resistance of fluoroquinolone antibacterials in hospital wastewaters in Hanoi, Vietnam. Chemosphere 72, 968–973

Feldmann DF, Zuehlke S, Heberer T (2008) Occurrence, fate and assessment of polar metamizole (dipyrone) residues in hospital and municipal wastewater. Chemosphere 71, 1754–1764

Gomez MJ, Petrovic M, Fernandez-Alba A, Barcelo D (2006) Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction and liquid chromatography-tandem mass spectrometry analysis in hospital wastewaters. J Chrom A 1114, 224–233

Hartmann A, Alder AC, Koller T, Widmer RM (1998) Identification of fluoroquinolone antibiotics as the main source of *umuC* genotoxicity in native hospital wastewater. Environ Toxicol Chem 17, 377–382

Hartmann A, Golet EM, Gartiser S, Alder AC, Koller T, Widmer RM (1999) Primary DNA damage but not mutagenicity correlates with ciprofloxacin concentrations in German hospital wastewaters. Arch Environ Cont Toxicol 36, 115–119

Heberer T (2002) Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: A review of recent research data. Toxicol Lett 131, 5–17

Heberer T, Feldmann D (2005) Contribution of effluents from hospitals and private households to the total loads of diclofenac and carbamazepine in municipal sewage effluents-modelling versus measurements. J Hazard Mater 122, 211–218. Erratum in: J Hazard Mater 127, 249

Jarnheimer P-Å, Ottoson J, Lindberg R, Stenstrom T-A, Johansson M, Tysklind M, Winner M-M, Olsen B (2004) Fluoroquinolone antibiotics in a hospital sewage line; occurrence, distribution and impact on bacterial resistance. Scand J Infect Dis 36, 752–755

Kümmerer K (2001) Drugs in the environment: Emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources – A review. Chemosphere 45, 957–969

Kümmerer K (2004a). Pharmaceuticals in the environment – Scope of the book and introduction. In: Pharmaceuticals in the Enviornment. Sources, Fate, Effects and Risks. Springer, Berlin

Kümmerer K (2004b) Resistance in the environment. J Antimicrob Chemo 54, 311–320

Kümmerer K, Henninger A (2003) Promoting resistance by the emission of antibiotics from hospitals and households into effluent. Clin Microbiol Infect 9, 1203–1214

Langford KH, Thomas KV (2009) Determination of pharmaceutical compounds in hospital effluents and their contribution to wastewater treatment works. Environ Int 35, 766–770

Larsson DGJ, de Pedro C, Paxeus N (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Haz Mat 48, 751–755

Lenz K, Koellensperger G, Hann S, Weissenbacher N, Mahnik SN, Fuerhacker M (2007) Fate of cancerostatic platinum compounds in biological wastewater treatment of hospital effluents. Chemosphere 69, 1765–1774

Li D, Yang M, Hu J, Ren L, Yu Z, Li K (2008) Determiantion and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and the receiving river. Environ Toxicol Chem 27, 80–86

Lin AY-C, Tsai Y-T (2009) Occurrence of pharmaceuticals in Taiwan's surface waters: Impact of waste streams from hospitals and pharmaceutical production facilities. Sci Tot Environ 407, 3793–3802

Lindberg R, Jarnheimer P-Å, Olsen B, Johansson M, Tysklind M (2004) Determination of antibiotic substances in hospital sewage water using solid phase extraction and liquid chromatography/mass spectrometry and group analogue internal standards. Chemosphere 57, 1479–1488

Mahnik SN, Lenz K, Weissenbacher N, Mader RM, Fuerhacker M (2007) Fate of 5-fluorouracil, doxorubicin, epirubicin, and daunorubicin in hospital wastewater and their elimination by activated sludge and treatment in a membrane-bio-reactor system. Chemosphere 66, 30–37

Muthanna TM, Plosz BG (2008). The impact of hospital sewage discharge on the assessment of environmental risk posed by priority pharmaceuticals: Hydrodynamic modelling and measurements. 11th International Conference on Urban Drainage, Edinburgh, Scotland

Ohlsen K, Ternes T, Werner G, Wallner U, Loffler D, Ziebuhr W, Witte W, Hacker J (2003) Impact of antibiotics on conjugational resistance gene transfer in *Saphylococcus aureus* in sewage. Environ Microbiol 5, 711–716

Reinthaler FF, Posch J, Feierl G, Wüst G, Haas D, Ruckenbauer G, Mascher F, Marth E (2003) Antibiotic resistance of E. coli in sewage and sludge. Water Res 37, 1685–1690

Schuster A, Hädrich C, Kümmerer K (2008) Flows of Active Pharmaceutical Ingredients Originating from Health Care Practices on a Local, Regional, and Nationwide Level in Germany—Is Hospital Effluent Treatment an Effective Approach for Risk Reduction? Wat, Air Soil Pollut 8, 457–471

Thomas KV, Langford (2007) Occurrence of pharmaceuticals in the aqueous environment. In Analysis, fate and removal of pharmaceuticals in the water cycle. Elsevier, Amsterdam

Thomas KV, Dye C, Schlabach M, Langford KH (2007) Source to sink tracking of selected human pharmaceuticals from two Oslo city hospitals and a wastewater treatment works. J Environ Mon 9, 1410

Chapter 15
Pharmaceuticals for Human Use: An Integrated Strategy for Reducing the Contamination of Water Bodies

Florian Keil

15.1 Introduction

Pharmaceuticals are in many cases an indispensable element of a comfortable and healthy life. Nevertheless, there is also a downside to the extensive use of medicinal products: their impact on the environment. Since the early 1990s, research findings have confirmed the occurrence of a wide range of human and veterinary active pharmaceutical ingredients (API) in surface waters, in groundwater and occasionally even in drinking water. Moreover, an increasing volume of data shows that specific substances can also trigger negative effects in animals and plants (for an up-to-date overview cf. Kümmerer 2008, SRU 2007). It still remains scientifically uncertain which risks to humans and the environment actually exist. It must be expected, however, that the problem will be aggravated in coming years, since the demographic development in Europe towards increasingly aging societies will bring with it an increase in consumption of medicinal products (see van der Aa and Kommer, Chap. 13, this book). The need for precautionary action is therefore more and more indicated.

Long-lasting strengthening of drinking water protection should receive particular attention in this respect. From a sustainability perspective this means already reducing contamination exposure of water bodies. This is the only way that the drinking water sources can be conserved for the benefit of future generations and at the same time environmental risks be minimised. At the present time there are no progressive and harmonised strategies in Europe for reducing contamination of drinking water and water bodies by APIs – a statement which appears to be equally true for other parts of the world. The existing legal provisions within the European authorisation process are limited to individual active ingredients and therein set a narrowly limited framework for measures of risk reduction. Therefore there is an urgent need for an integrated strategy that strengthens the idea of precaution in dealing with the

F. Keil (✉)
Institute for Social-Ecological Research (ISOE), Frankfurt/Main, Germany
e-mail: keil@isoe.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_15,

undesired impacts of the use of pharmaceuticals for water quality while at the same time taking into account their high individual and societal benefits.

This requirement was incorporated in the German research project *start.* Confining itself to pharmaceuticals for human use the project investigated three spheres of activity in which precautionary action can be applied: "Drug Development", "Handling of Drugs" and "Technical Emissions Control in Urban Water Management". This approach is based on the life cycle of a medicinal product and can be considered as a possible framework for conceptualising the vision of Sustainable Pharmacy. Although *start* focussed on the situation in Germany, most of its results can be principally transferred to other industrialised countries as well.

Starting with a brief summary of the current statutory regulations in Europe and the role of the precautionary principle, the chapter will introduce catalogues of options of action for each of the three spheres of activity. This is followed by a critical discussion about the prospects for implementing the proposed options of action. The chapter will conclude with remarks on how an integrated approach towards reducing the contamination of water bodies can be put into effect.

15.2 The Current Legal Situation

In the course of the market authorisation of a human pharmaceutical in Europe, an environmental risk assessment (ERA) has been compulsory since 1993 (directive 93/39/EC) – a regulation that since 2004 also applies to generics (directive 2004/27/EC and 2001/83/EC, respectively). An ERA is not required for pharmaceuticals which were authorised before this regulation came into effect. A consistent technical standard for drug manufacturers on how to implement the ERA has, however, only been available since December 1, 2006, in the form of a guideline provided by the European Medicines Agency (EMEA 2006). This guideline is applied both in the pan-European and the national authorisation of a drug. In Germany the technical control of an ERA is enforced by the German Federal Environment Agency in accordance with the competent authorisation authority (German Federal Institute for Drugs and Medical Devices).

According to the European guideline, the ERA consists of a two-phase procedure (EMEA 2006). In the first phase the expected concentration of the new substance in surface waters is assessed based on model assumptions (*Predicted Environmental Concentration*, PEC). In the case when the PEC value is below the threshold of 0.01 μg/l no risks for the environment are assumed and the ERA is terminated. In the other case, phase two is initiated which requires the acquisition and assessment of experimental data on the eco-toxicity and a refined fate analysis of the API in question. These data lead i.a. to the determination of a threshold concentration below which no negative effects for aquatic organisms are to be expected (*Predicted No Effect Concentration*, PNEC). In the case when the (refined) PEC exceeds the PNEC, an environmental risk for the new substance is assessed. Exceptions from this two-phase procedure exist for APIs whose specific mechanism of action makes

a particular risk for the environment likely (carcinogenic, mutagenic and reprotoxic substances). For those APIs the detailed hazard and risk assessments of phase two are always mandatory. As a general precautionary measure the EMEA guideline recommends that package leaflets should include a statement on the proper disposal of medicinal waste.

It is crucial to note that if, in the framework of the ERA, an environmental risk is identified, authorisation of the human medicinal product can explicitly not be denied. In this case only precautionary measures for mitigating the risk may be required. The actual options for the competent authorities to enforce such measures are currently strongly limited, however. In practice they are confined to information about the assessed environmental risks on package leaflets and product instructions for physicians and pharmacists. For veterinary pharmaceuticals the legal situation is different. Here authorisation may be denied or limited to certain application areas if evidence for an environmental risk exists (directives 2004/28/EC and 2001/82/EC respectively).

There are currently no compulsory threshold values for the occurrence of APIs in surface waters and in groundwater on a European level or in Germany. However, their definition is in principle legally possible, for example within the context of the European Water Framework Directive. Medicinal products are explicitly excluded from the central provisions of the new European Community Regulation on chemicals, REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), because they are separately handled by the aforementioned directives.

On a European level (in the framework of the Drinking Water Directive 98/83/EC) there is to date no threshold value for pharmaceutical residues in drinking water (this applies both to human and to veterinary medicinal products). Analogously, there are currently no compulsory threshold values for APIs defined in the framework of the German Directive on the Quality of Water for Human Consumption. Here only the non-toxicologically inferred and non-compulsory precautionary threshold value of 0.1 μg/l recommended by the German Drinking Water Commission applies to drugs and other as yet unevaluated substances (Umweltbundesamt 2003b).

With the amendment of the EU directive on the creation of a Community Code Relating To Medicinal Products For Human Use (2004/27/EC), an article for establishing collection systems for unused or expired medicinal products was incorporated which should make possible proper disposal of the substances (Article 127b); (see Castensson and Ekedahl, Chap. 12 and Vollmer, Chap. 11, this book). All member states were required to provide such systems by October 2005. In Germany there has been a take back system via pharmacies since 1995. This system was originally set up so that manufacturers of pharmaceuticals and other medicinal products could comply with their obligations under the "Verpackungsverordnung" (German Regulation on Packaging) with respect to the recovery of potential recyclables. Until May 2009 about three quarters of all pharmacies in Germany were connected to a take-back system. However, with the fifth amendment of the Verpackungsverordnung from April 2008, the operation of the take-back system was considered inefficient by the main German provider VfW Remedica. As a

consequence, VfW Remedica withdrew from its contract with the German pharmacies in May 2009. By the time of writing this chapter, no agreement was reached on a renewed nationwide take-back system.

15.3 Risk and the Precautionary Principle

In order to assess a risk to humans or the environment it is necessary – in the classical approach – to establish a causal relationship between an agent and an observed harmful effect. In risk assessment of chemicals generally, and particularly in the case of APIs, this is manifestly possible only in rare cases (see Sumpter, Chap. 2, this book). There are essentially two reasons for this. On the one hand, due to the great variety of substances, negative effects such as the observed feminisation of male fish (Jobling et al. 1998) can be triggered by different substances acting on their endocrine system, or can also be the result of the combined and simultaneous action of several substances ("cocktail effect"). On the other hand, long periods of time can pass between the causation and the observed effect. The identification of causal relations for this type of chronic effects is scientifically markedly difficult. In such a situation of scientific uncertainty the precautionary principle as a legal instrument for dealing with a possible hazardous situation comes into play.

Since the Maastricht EU Treaties of 1992 (Treaty on the European Union, 92/C 191/01, Article 174), the precautionary principle is one of the most important legal policies in European environmental legislation. It legitimises decisions, and the conduct based thereon, even when possible effects harmful to humans and to the environment are known, but their risk cannot be determined with sufficient certainty through scientific evaluation (European Commission 2000). The incorporation of the precautionary principle is based on a normative claim that requires preventive creation of latitude and safety margins, even for risks that may be characterised as such only in the future (von Schomberg 2006). The regulations currently in force at EU level – particularly the obligatory performance of an ERA as part of the first time authorisation of a pharmaceutical – must be viewed in the context of an invocation of the precautionary principle.

In *start* a round of talks with experts from pharmaceutical industry, water management, medical and pharmacy associations, health funds and authorities was held. Here, it was agreed upon that the precautionary principle should play a decisive role in dealing with drinking water contamination by active pharmaceutical ingredients. Disagreement was, however, on the proportionality of concrete precautionary measures in view of the existing uncertainties in risk assessment. This dissent has to been seen as a direct expression of the high societal benefit that is connected with the development and the use of drugs. Precautionary measures for reducing water contamination should therefore neither hamper innovations in drug development nor impair the quality of medical care (for example in that particular measures cannot be integrated into the complex professional routine of physicians). In other words, a

precautionary approach must be configured such that the individual actor's capacity to act and innovate is preserved or, if possible, even increased.

15.4 Options of Action for Reducing the Contamination of Water Bodies

The starting point in *start* for determining options of action for reducing the contamination of water bodies by APIs was the precautionary and long-term strengthening of drinking water protection. In the spirit of the life cycle-oriented research approach, the principle of starting as much as possible at the source of entry of the active ingredients – that is already at the development and utilisation of the substances – was employed for this purpose. Employing this principle allows the development of sustainable problem solutions – solutions that preserve our drinking water sources for the benefit of future generations and simultaneously reduce environmental risks. In the subsequent sections a catalogue of options of action in each of the three spheres of activity (see Table 15.1) is introduced.

15.4.1 Sphere of Activity "Drug Development"

The primary aim of drug development is to achieve high efficacy along with as little adverse drug reactions as possible. One consequence of this is that the agent molecules are optimised for stability – a fact that usually prevents their biological degradation in today's conventional sewage treatment plants. Now this goal and rapid biological degradation in the environment are not necessarily in conflict, for whether a molecule is degraded slowly or rapidly does not depend solely on its structure (see Kümmerer, Chaps. 1 and 9, this book). Indeed, it depends also, and crucially, on the conditions in the medium considered, such as frequency and intensity of light, pH-value, temperature or type and number of microorganisms present (Kümmerer 2007). These conditions differ considerably in the human body and in the environment. In drug development such differences can thus be used if it is known which chemical moieties of molecules are particularly favourable to the application desired and which are particularly bad for rapid degradation in the

Table 15.1 Spheres of activities for reducing contamination of water bodies

Drug development	Handling of drugs	Emissions control
Development of active pharmaceutical ingredients that are optimised both for efficacy in humans and degradability in the environment	Change in current prescription practices, utilisation, and disposal patterns towards a greater degree of environmental compatibility	Optimisation of wastewater disposal, wastewater treatment, and drinking water processing in the removal of pharmaceutical residues

environment. Given this knowledge it is basically possible to apply a new design principle: by means of targeted intervention in the molecular structure both the degradation of a "green" pharmaceutical in the environment and its functionality can be optimised (Kümmerer 2007, see Kümmerer, Chap. 9, this book).

For the pharmaceutical industry, this action perspective means no longer relating sustainable corporate management solely to raw materials and production processes but, more emphatically, to the product itself (see Läufer, Chap. 5, this book). This type of corporate management corresponds to the model of Sustainable Pharmacy. Besides the question of their economic market potential, there are several factors that affect the chances of a green product policy in pharmaceutical industry. These include the further development of computer-assisted methods for molecular design, the implementation of the new design principle in research and development and pre-eminently the early availability of successful examples of green active ingredients from as many different areas of application as possible – wherein "success" means that the green pharmaceuticals are not only better for the environment but have equally good or even better application properties than conventional ones (Kümmerer 2007).

Table 15.2 shows a catalogue of options of action by means of which the development of green APIs can be promoted (Kümmerer and Schramm 2008). They aim primarily at anchoring the new design principle as a fundamentally new mindset and approach in research and development practice. In addition, incentives are introduced that can make a green product policy attractive for medicinal product manufacturers.

15.4.2 Sphere of Activity "Handling of Drugs"

In contrast to other product areas, environmental aspects have previously hardly played a role in prescribing or purchasing, use or disposal of medicinal products. In the scenario of the substance life cycle, however, the phase of handling drugs also provides approaches for effective options of action for reducing the contamination of water bodies (see Götz and Deffner, Chap. 10 and Wennmalm and Gunnarsson, Chap. 16, this book). In general, these can be implemented at two points: on the one hand in reducing the consumption of pharmaceuticals, and on the other hand in the avoidance of medicinal wastes that may be improperly disposed of via domestic wastewater (or in ensuring proper disposal of medicinal products, respectively).

The use of medicinal products is associated with high and undisputed individual and social benefits. Moreover, a medical decision for a medicinal therapy generally depends on a number of factors that must be weighed against each other. Here, in each individual case, priority is given to the best possible strategy for curing or palliation of a disease. When in doubt, the rule is "health protection before environmental protection". At the same time, it must also be assumed that further regulations in an already heavily regulated system that are aimed at an objective that is perceived to be secondary will encounter opposition, particularly with physicians. Measures that

Table 15.2 Options of action in the sphere "drug development"

Research and development	
Research funding programmes	Independent research institutions and medicinal product manufacturers are supported in the development of green active pharmaceutical ingredients
Evaluation of the programmes	The focus of the evaluation will be the significance of a green product policy for the innovative capacity of medicinal product manufacturers
Examples of success	In order to promote a green product policy in the pharmaceutical industry a list of successful examples of green active ingredients will be published
Adjustment of university education	
Research and education foci	Their set-up should promote rapid implementation of the new design principles in chemistry and pharmacy
Change in the legal framework	
Extension of patent duration	Privileging green active ingredients would create stimuli for innovation and increases economic security when pursuing this development strategy
Change of authorisation	Green active ingredients become privileged through tightened coupling of the environmental risk assessment and the medicinal product authorisation
Communication measures	
Awards and competitions	These should promote the issues of "Green Pharmaceuticals" and "Sustainable Pharmacy" in research, education, and in the general public
Public relations campaign	By running campaigns for Sustainable Pharmacy and the advantages of green drugs, their acceptance and marketability would be increased

are intended to make the handling of drugs more environmentally compatible must therefore satisfy three prerequisites:

- They must not result in a quality loss in prevention and therapy
- They must be integrable into the complex professional routine of physicians and pharmacists
- They should co-operate with already societal desirable plans for reform in the healthcare system.

Behavioural changes that should contribute to a reduction in contamination of water bodies, however, require a corresponding awareness of the problem, particularly if they are to be implemented voluntarily. Empirical studies in *start* have however shown that physicians and pharmacists have previously hardly confronted the consequences of consumption and disposal of medicinal products for water quality (see Götz and Deffner, Chap. 10, this book).

Table 15.3 Options of action in the sphere "handling of drugs"

Policy frameworks	
Environmental objective: protection of water bodies	Safeguarding surface and groundwater from contamination by pharmaceutical residues is defined as an environmental objective
Increasing problem awareness	
Discussion opportunities	Targeted information opportunities promote opinion-formation in physicians and pharmacists with respect to the topic of contamination of water bodies by active pharmaceutical ingredients
Professional retraining	The topic of contamination of water bodies by active pharmaceutical ingredients will become an integral part of the retraining of physicians and pharmacists
Change in prescription practices	
Environmental classification	An environmental classification for human pharmaceuticals allows physicians to prescribe environmentally compatible active ingredient alternatives
Drug consumption	Reducing drug consumption by increasingly prescribing where possible non-medicinal forms of therapy that generally promote health
Avoidance of medicinal product wastes	
Information on drug consumption	Control of patient demand by creating cost and quantity transparency for insurants in statutory health insurance
Package sizes	Offer of variable package sizes, starter packs for chronic diseases and dispensing of partial quantities (for example tablet blisters)
Disposal of unused or expired medicinal products	
Disposal standard	Creation of a consistent and compulsory disposal standard by return to pharmacies and simplification of the take-back system for pharmacies
Education and labelling	Sweeping information campaigns relating to proper disposal as well as disposal instructions on medicinal product packaging and package leaflets

In Table 15.3 a catalogue of options of action is presented, by means of which the handling of drugs can be structured to be more environmentally compatible (Deffner and Götz 2008). It addresses to official bodies, health funds, the different organisational levels of the medical and pharmacy associations, practicing physicians and pharmacists themselves, patients and the manufacturers of medicinal products. It must be considered that options of action that can contribute directly to a reduction of contamination of water bodies can be realised only if appropriate foundations are laid beforehand. Policy frameworks that highlight contamination of water bodies by APIs as a societal problem to be reckoned with, as well as dissemination of knowledge and information on the subject are part of this. In this sense, the options of action presented strategically build upon each other.

15.4.3 Sphere of Activity "Technical Emissions Control in Urban Water Management"

Even if green pharmaceuticals become more and more available and the use of drugs becomes more environmentally compatible, environmental technology for reducing the occurrence of active ingredients in water bodies will remain indispensable in the foreseeable future. APIs, however, represent only part of the spectrum of organic trace contaminants that present urban water management with technical problems as regards their removal from waste and raw waters. Investments in specific upgrades and improvements of the existing systems and processes of wastewater disposal, wastewater treatment and drinking water processing must therefore always be viewed in connection with the solution of more extensive substance problems. Options of action for reducing water body contamination with trace contaminants can be approached basically at three levels:

- Reduction of substance emissions into municipal wastewater
- Wastewater treatment in sewage treatment plants
- Drinking water processing in water works.

The goal of sustainable emissions control (see Table 15.4) should be to remove problematic substances ideally before they enter municipal sewage (Püttmann et al. 2008). A corresponding long-term strategy is the gradual implementation of sustainable sanitation concepts. These are based on the idea of separating the different waste water fractions at the location where they are generated, i.e. service water and toilet water are collected and treated separately. Since concentrations of APIs in undiluted toilet water are higher, available treatment techniques – like membrane bioreactors or fermentation methods – can, for physical reasons, be operated at significantly increased levels of efficacy. After being purified at the point of origin the different waste water fractions can either be discharged into the municipal sewer network or be directly reused. These concepts are of particular importance because they can be coupled with other sustainable techniques like energy recovery from fermentation processes in the faeces fraction of toilet water or with the recycling of finite and already scarce resources like phosphorus from urine.

In any comprehensive survey of possible measures the use of advanced techniques in sewage treatment plants should also be included. However, none of the currently discussed techniques, such as activated carbon filtration, membrane filtration or ozonation, is able alone to eliminate the whole known spectrum of APIs (Püttmann et al. 2008). Data from large scale pilot plants are needed in order to provide possible site specific recommendations. In Germany the majority of water works using surface water or bank filtrate as raw water sources apply activated carbon filtration (sometimes together with ozonation). Since measures at the sewage treatment plants as well as the implementation of sustainable sanitation concepts would become effective only over a mid- to long-term perspective, it should be

Table 15.4 Options of action in the sphere "technical emissions control in urban water management"

Reduction of emissions of active ingredients into municipal sewage	
Separation of sewage component flows	By separating sewage component flows and their optimised treatment at the point of origin, municipal wastewaters can be relieved
Hospital wastewaters	In case of a strong contamination with problematic substances, a separate collection and treatment should be established before discharge into the municipal sewage system
Wastewater treatment in sewage treatment plants	
Assessment of advanced technologies	As soon as data from large-scale experiments with powdered activated carbon in sewage treatment plants are available a comprehensive assessment should be carried out
Increase of activated sludge age	By increasing sludge age to about 10 days, an improvement in the biological degradation of some active pharmaceutical ingredients would be possible at low cost
Drinking water processing in water works	
Activated carbon filtration	Water works that directly or indirectly use contaminated surface water and do not yet use activated carbon filtration should upgrade accordingly

examined whether individual water works need to upgrade accordingly in order to enhance drinking water protection (e.g. with respect to a quality goal of 0.1 μg/l).

15.5 Discussion

In the three spheres of activity "Drug Development", "Handling of Drugs" and "Technical Emissions Control in Urban Water Management" there is a broad spectrum of options of action that can contribute to a reduction in water body contamination (start 2008). But what can actually be accomplished with implementation of these options of action and what would be the consequences of concentrating only on one sphere of activity in the problem solution? These questions were examined in the framework of *start* using a formal assessment method wherein different criteria like efficacy, cost and acceptance of a measure were evaluated. Because of the complexity of the individual spheres of activity and the data situation – which in many parts is insufficient – work generally had to be done only with orientation values and qualitative information. The central finding was that a sustainable contribution to solving the problem cannot reside in one of the three spheres of activity alone – a finding that was confirmed by the participants in the *start* expert dialogue. The most important aspects of this study are summarised below for each sphere of activity.

15.5.1 Sphere of Activity "Drug Development"

The fact that "greening" of molecules is in principle also applicable to other classes of chemicals – whereby those that reach water bodies when used as intended or because of their open application (cleaning agents, pesticides, personal-care products, for example) are of particular interest – is of special importance to the implementation of the new design principles. Up to now an orientation towards green product innovations was hardly a core element of sustainable corporate management in the chemical industry (as for the situation in pharmaceutical industries, see Taylor, Chap. 7, Läufer, Chap. 5 and Triggle, Chap. 3, this book). It was, however, emphasised from different parties that such an approach is future oriented. In 1994, the committee of inquiry of the 12th German Bundestag "Protection of Humans and the Environment" developed perspectives for a sustainable handling of chemical substances, in that the significance of the environmentally compatible design of chemicals for a sustainable development was emphasised (Enquête-Kommission 1994). In the Sixth Environmental Action Program, the European Parliament and the European Commission formulated inter alia the partial objective of producing and using chemicals within one generation only so that they have no negative effects on the environment (Decision no 1600/2002/EC). The German Advisory Council on the Environment of the German Federal Government anticipates a rise in innovation and increasing competitive advantages over the medium to long term on markets for environmentally and health-friendly products (SRU 2003).

When estimating the costs of setting up and implementing the new design principles it must be taken into account that the development of new active ingredients is urgently imminent in different indication groups. Investment in drug development is therefore necessary anyway. Consideration of green options is as yet hardly associated with relevant additional costs compared to the overall outlay. In terms of the options of action presented, the main costs are attributed to funding of research. But these pay off in the reinforcement of top-shelf technology in pharmaceutical research and its sustainable orientation. The programs to be established – that are equally aimed at university and industrial research – would have to be jointly borne by the economy and the public. In order to achieve convincing results, such a phase of intensive research funding would have to extend over a period of 10−15 years, according to expert opinion.

The promotion of sustainable design principles and the use of new technologies associated with them will create an essentially different understanding for innovations in the pharmaceutical industry and possibly also new market opportunities. Here, the concept of "Sustainable Pharmacy" should be established as a long-term strategy or as a model in exploratory pharmaceutical industry. This represents a big challenge. On the one hand – in contrast with today – a clear longer-term action orientation in the field of research and development is necessary for achieving this. On the other hand, there is currently an innovation crisis in the pharmaceutical industry. In this situation there is the risk that long-term development perspectives will regress vis-à-vis measures for fulfilling short-term expectations of returns. We assume that – both for the chemical and for the pharmaceutical industry – it is this very

strategy that aims at sustainable design principles which provides a forward-looking way out of this crisis. It allows for a worldwide product accountability, since the green active ingredients and chemicals with less consequences for humans and the environment can also be used in regions in which there is no technically sophisticated wastewater purification or none at all.

15.5.2 Sphere of Activity "Handling of Drugs"

An essential part of the identified options of action aims at generating problem awareness, the provision of information and stimulating motivation for bringing about behaviour change in handling of drugs. Along with its importance to the implementation of very practical measures such as the use of an environmental classification in the professional routine, these activities also have a superordinate meaning: they can have a positive effect on the overall perception of the problem and thus promote implementation of measures in other spheres of activity. It is very difficult to estimate the degree and the timeframe in which practical effective behaviour changes with physicians is possible. Experiences in Sweden show that the environmental classification introduced there in 2004 is adapted by a majority of physicians (Wennmalm and Gunnarsson 2008, see Wennmalm and Gunnarsson, Chap.16, this book). This experience can, however, be transferred only conditionally to Germany. One should be concerned that, in view of the bemoaned over-regulation of professional routine, this type of instrument will be perceived as yet another burden. The upcoming "generation turnover" in surgeries – which in view of the age structure of the medical community will probably take place in the next 10 years – provides one perspective, however. If the subject is already intensively integrated in university education, acceptance of an environmental classification and other options of action will be additionally increased in practice.

The discussed options of action relating to changing prescription practices and for avoiding medicinal product waste can, in cooperation with overlapping reform measures in the healthcare system, contribute to a more rational use of medicinal products. Here, too, it's hardly possible to estimate reliably using available data what volume of medicinal products can be saved by replacing them with equally satisfactory care – such as by prescribing non-medicinal forms of therapy. It must be considered that the instruments presented do not apply equally to all indication groups. The consumption volumes of cytostatics but also of diagnostics (X-ray contrast media, for example) will probably remain virtually unaffected. A rough estimate of how strongly the entry of APIs into domestic wastewater due to improper disposal can be reduced is, in contrast, feasible. Estimates regarding the annual quantity of medicinal product waste in Germany are 10−20% of the total volume consumed – which at 38,000 t/year (in 2001, Umweltbundesamt 2003a) is equivalent to 6,000 t. If the figures from the *start* survey on the disposal behaviour of the Germans are used as the basis (Götz and Keil 2007), it follows that probably around 1,000 t go directly into domestic wastewater via the drain and toilet – a number that

can be clearly reduced over the medium term by the identified options of action for improving disposal.

The direct costs arising in the case of implementation of the discussed options of action will be contained within comparatively manageable limits because communicative measures and capacity building are in the foreground. Realisation of discussion opportunities and supplementation of professional retraining for physicians and pharmacists, as well as the implementation of information campaigns relating to proper disposal of unused or expired medicinal products, are clearly less than ten million Euros annually according to initial estimates – whereby investment periods of different lengths must be considered.

15.5.3 Sphere of Activity "Emissions Control in Urban Water Management"

Prospects for implementation of options of action in this area depend essentially on the answer to the question of how technical options of advanced wastewater treatment at municipal sewage treatment plants score in a comprehensive performance assessment. Emphasis should be placed on working out such an assessment based on a cost-benefit or multi-criteria analysis. Regardless of the outcome of this evaluation, however, there are aspects that should be considered critically in the discussion about solutions in the area of municipal wastewater. In cities with combined sewage systems, domestic and industrial wastewater is mixed with rain water. In the event of overloading the sewage system or the retention ponds due to heavy rains, the wastewater is discharged untreated into water bodies – an event that could increase in some regions in the future due to climate change. The relevance of this source of entry should be specifically examined and, if necessary, solutions worked out for its resolution before an expensive upgrading of the sewage system is carried out.

In addition, in the decision-making process for advanced sewage treatment, it should be considered that limitation to the use of a single technology may critically limit the effectively treatable range of substances. Focusing on, for example, powdered activated carbon would only solve the problem of APIs that deposit easily on the carbon particles due to their physical-chemical properties. There are, however, other substances such as the X-ray contrast agent amidotrizoic acid that is difficult to remove from water using this process. The acceptance of cost-intensive upgrading of sewage treatment plants would suffer considerably in the population if, despite the increased expense, APIs and other trace contaminants were to reach water bodies and even drinking water. Moreover, it cannot be ruled out that new substances that reach wastewater only in the future will have properties that render them "insensitive" to the selected treatment technology. This problem would probably be confronted only with a combination of technologies, which would then come along with a further cost increase and additional environmental impacts (increasing raw material input and energy demand). Summarising, this means that precautionary measures for drinking water protection through water works remain – at least in the mid-term – indispensable.

Focussing on sewage treatment plants and centralised wastewater disposal also raises other fundamental questions. This is because, in the view of many scientists, urban water management is facing a paradigm change that leads away from the central system towards substance flow separation and compartmental wastewater treatment. Even if an effective and at the same time economic solution was to be identified for sewage treatment plants, stepwise implementation of options of action in the area of sustainable sanitation systems is trendsetting. It corresponds to the principle of retaining the contaminants at the source and furthermore provides latitude for sustainable development (energy abstraction from wastewater and recycling of scarce resources like phosphorous from urine). Beyond that, it has to be kept in mind that advanced technical solutions in urban water management which depend on a centralised system are not globally applicable. Focussing on these techniques and thus neglecting other options of action like developing green pharmaceuticals will contribute to sourcing out the problem to countries which lack the infrastructure or simply the resources to implement them.

In the area of emissions control, a locally dependent combination of measures for reducing water body contamination presents itself as the most realistic perspective. In implementing measures water bodies relevant for drinking water abstraction should receive priority.

15.6 Towards an Integrated Strategy

The previous considerations already indicate that a comprehensive solution of the problem cannot reside in one sphere of activity alone. Even if all courses of action were exhausted in one sphere, not all substances and all entries would be reached. This appraisal becomes even more concrete when questions of causation and responsibility are discussed. Formally considered, the cause of the problem is the healthcare system. Here the pharmaceuticals are used for treating or preventing diseases and ultimately are released into the environment by one route or another. In the sense of the polluter pays principle, it could be argued: The costs of reducing water body contamination by APIs must be borne by the healthcare system. In fact, it can be assumed that precisely if it were a question of the implementation of environmental technology, the associated transfer of the environmental costs from the healthcare system to urban water management would be viewed as a violation of the polluter pays principle – a position which would at least hamper acceptance for legally bound measures in this area.

Increased acceptance can instead be achieved if the healthcare system is integrated into a comprehensive solution right from the start and thus would bear a portion of the costs. The previously discussed options of action relating to the handling of drugs are designed such that this effect would probably be achieved, without concomitantly imposing unbearable burdens on a system that has reached its financial limit anyway. If at the same time the pharmaceutical industry were to undertake visible efforts at reducing the undesirable consequences of its products

on water bodies by developing greener pharmaceuticals, latitude emerges for a joint effort towards a sustainable and effective reduction of water body contamination by APIs and the risks to humans and the environment that possibly come along with it. Ultimately all citizens and professionals in the different areas benefit from pharmaceuticals and are concomitantly co-causing the problem through their behaviours. Its solution should therefore follow in shared responsibility on the basis of precautionary thinking.

15.7 Conclusions

Comparing the problem of pharmaceuticals in the environment with, e.g. the pesticide problem, the following question might emerge: why not enforce the relevant statutory regulations such that future risks for humans and the environment can effectively be minimised? Considering this idea more closely, it soon becomes clear that a purely legal approach will quickly confront its limits. The main argument for this is that denial of authorisation for a therapeutically effective drug due to environmental concerns would have far reaching ethical implications. Certainly, there will be cases for which the efficacy or indication of the new drug is arguable and a ban appears reasonable on the basis of a thorough cost-benefit-analysis. In most cases, however, denial of authorisation or effective constraints for application due to environmental concerns will hardly be justifiable. For illustration consider the case of a new medicinal product for cancer therapy.

Legally bound measures in the area of water protection – e.g. the determination of quality goals for individual APIs within the implementation of the EU Water Framework Directive – are however possible and meaningful (an approach currently discussed with respect to the anti-inflammatory agent diclofenac and the anti-epileptic carbamazepine). A comprehensive solution to the problem isn't yet feasible with this approach. If the measure remains isolated the limits to the denial of authorisation for a specific API discussed above will result in assigning urban water management the sole responsibility for problem solving.

Nevertheless, it is decisive for the success of an integrated strategy that different departmental polices at the national and regional levels participate proactively in the implementation of the recommended options of action. Here, "proactive" may not necessarily mean that the government policy generally provides the stimulus. Rather, it should support the relevant actors in the realisation of options of action, in that it more emphatically takes up the theme of "drinking water and water body contamination by pharmaceuticals" in a solution perspective.

Water is a special life resource that deserves our particular attention. Past experiences in interacting with the risks posed by substances have shown that remedial problem solving is generally more expensive for society than pre-emptive, precautionary action. If precaution is driven by all participating actors in the sense of shared responsibilities, not only can the "costs of error" be minimised, but potentials for social and technical innovation can even be opened up. The developed strategy

points in this direction. Finally, it is essential to note that latitude in coping with water contamination by APIs still looms large enough today so that we can learn from old mistakes.

Acknowledgments The project *start* ("Management Strategies for Pharmaceutical Residues in Drinking Water") was funded between October 2005 and May 2008 by the German Federal Ministry of Education and Research (contract no. 07VPS16). The author wishes to thank the *start* project team for making this publication possible: Gotthard Bechmann, Christian Büscher, Jutta Deffner, Petra Döll, Konrad Götz, Michaela Kawall, Klaus Kümmerer, Alexandra Lux, Jörg Oehlmann, Ulrike Schulte-Oehlmann, Wilhelm Püttmann, Engelbert Schramm, Irmgard Schultz and Alexandra Titz.

References

Deffner J, Götz K (2008) Handlungsoptionen für einen umweltfreundlicheren Umgang mit Arzneimitteln. Umweltwiss Schadst Forsch 20, 238−248 in German (Engl. abstract)

Enquête-Kommission "Schutz des Menschen und der Umwelt" (ed.) (1994) Die Industriegesellschaft gestalten. Perspektiven für einen nachhaltigen Umgang mit Stoff- und Materialströmen. Economica, Bonn

European Agency for the Evaluation of Medicinal Products (EMEA) (2006) Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. Doc. Ref. EMEA/CHMP/SWP/4447/00. 01.06.2006, London

European Commission (2000) Communication from the Commission on the Precautionary Principle, (COM 2000/001), Brussels

Götz K, Keil F (2007) Medikamentenentsorgung in privaten Haushalten: Ein Faktor bei der Gewässerbelastung mit Arzneimittelwirkstoffen? Umweltwiss Schadst Forsch 19, 180–188. In German (Engl. abstract)

Jobling S, Nolan M, Tyler CR, Brighty G, Sumpter JP (1998) Widespread sexual disrup-tion in wild fish. Environ Sci Technol 32, 2498−2506

Kümmerer 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 Chem 9, 899–907

Kümmerer K (ed.) (2008) Pharmaceuticals in the Environment. Springer, Heidelberg, New York (3rd, revised and enlarged edition)

Kümmerer K, Schramm E (2008) Arzneimittelentwicklung: Die Reduzierung von Gewässerbelastungen durch gezieltes Moleküldesign. Umweltwiss Schadst Forsch 20, 249−263. In German (Engl. abstract)

Püttmann W, Keil F, Oehlmann J, Schulte-Oehlmann U (2008) Wassertechnische Strategien zur Reduzierung von Gewässerbelastungen durch Arzneimittelwirkstoffe. Umweltwiss Schadst Forsch 20, 209−226. In German (Engl. abstract)

SRU (German Advisory Council on the Environment) (2003) Zur Wirtschaftsverträglichkeit der Reform der Europäischen Chemikalienpolitik. Stellungnahme, Berlin

SRU (German Advisory Council on the Environment) (2007) Pharmaceuticals in the Environment. Statement. Berlin

Umweltbundesamt (German Federal Environment Agency) (2003a) UBA Forschungsvorhaben Mengenermittlung und Systematisierung von Arzneimittelwirkstoffen im Rahmen der Umweltprüfung von Human- und Tierarzneimitteln gemäß § 28 AMG (FKZ 299 67 401/1). Umweltbundesamt Berlin. In German (Engl. abstract)

Umweltbundesamt (German Federal Environment Agency) (2003b) Bewertung der Anwesenheit teil- oder nicht bewertbarer Stoffe im Trinkwasser aus gesundheitlicher Sicht Empfehlung des Umweltbundesamtes nach Anhörung der Trinkwasserkommission beim Umweltbundesamt. Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 2003, 46, 249–251. In German

von Schomberg R (2006) The precautionary principle and its normative challenges. In: Fisher E, Jones J, von Schomberg R (eds.) Implementing the Precautionary Principle: Perspectives and Prospects. Edward Elgar, Cheltenham, UK and Northampton, MA, Chap. 2, pp. 19−42

Wennmalm Å, Gunnarsson B (2008) Mitigation of pharmaceutical outlet into the environment – experiences from Sweden. In: Kümmerer K (ed.) Pharmceuticals in the Environment. Sources, Fate, Effects and Risk. Springer, Heidelberg, New York

Chapter 16
Experiences with the Swedish Environmental Classification Scheme

Åke Wennmalm and Bo Gunnarsson

16.1 Background

The European Commission launched, in November 2001, a proposal for a new directive on medicinal products for human use within the community. In accordance with the EU process for co-decision, the proposal was submitted to the Parliament for reading. In that process a suggestion was raised in the Parliament that the Commission should develop an environmental classification system for human medicinal products. The rationale behind the suggestion was the emerging evidence that used human medicinal products often reach the aquatic environment, after normal use or after disposal of unused or expired medicines. The suggestion from the Parliament on environmental classification of human medicines was not accepted by the Commission at that time, but the rejection was considered "soft", i.e. a door was kept open that such a system might be considered later.

Two Swedish health care parties, Apoteket AB (ABA) and Stockholm County Council (SCC) followed the Parliament reading of the Commission proposal closely, and considered the suggested amendment to introduce environmental classification of medicines most relevant. Since the Commission found itself unable to accept the suggestion, ABA and SCC decided to establish a customer driven local environmental classification system for human medicinal products in the Stockholm region. The idea was to ask producers to deliver environmental data on their products in connection with the procurement process of medicines for public health care. The first enquiries were sent to the producers in connection with the 2003 procurement of medicines.

Å. Wennmalm (✉)
Stockholm County Council, S-104 22 Stockholm, Sweden
e-mail: ake.wennmalm@sll.se

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_16,

16.1.1 The Stockholm Model for Environmental Classification of Human Medicines

Initially, the intention was to create a risk classification system for the Stockholm region, based either on measured environmental concentrations (MEC) of intact pharmaceutical substances in the recipient or on predicted environmental concentrations (PEC). PEC was planned to be based on composed sales from all producers of a substance to be risk classified, and on the actual volumes of water in the Stockholm recipient. However, contacts with proper authorities and eco-toxicologists eventually yielded in a shift in preference towards a system based on hazard, instead of risk. Two arguments were considered critical in favouring assessment of hazard instead of risk. First, risk is always connected to specific local or regional conditions with respect to consumption of medicine and volume of recipient receiving the effluent from the sewage treatment plant. Thus, risk varies from one place to another. This implies that a risk assessment performed on a national basis may be of limited local value. Second, risk assessments would be based mainly on acute eco-toxicity data, inasmuch as figures on chronic eco-toxicity are usually not available. Since data on chronic eco-toxicity regularly reveal lower no-effect concentrations than acute data, assessments based on the latter would frequently end up with inadequately low risk probabilities.

Thus, the Stockholm model for environmental classification of human medicines became a pure hazard classification, based on the variables persistence (P), bioaccumulation (B) and eco-toxicity (T) to aquatic organisms. Classification was based on generally accepted test methods, preferably in accordance with the OECD technical guidelines (OECD).

To simplify the presentation of the hazard assessment to health care categories not familiar with environmental hazard assessments, a score system was developed. In this system persistence and potential to bioaccumulation were each given a score of 0 or 3, depending on test result. Toxicity was given a score of 0–3, depending on test result. The test results qualifying for the different scores are presented in Table 16.1.

Table 16.1 Scoring of the hazard variables persistence, bioaccumulation and eco-toxicity in the Stockholm model for environmental classification of pharmaceutical substances

Persistence		
– Easy biodegradable	>60%/28 days	0
– Not biodegradable	<60%/28 days	3
Bioaccumulation (LC/EC/IC_{50})	Log $K_{O/W}$	
– Potential to bioaccumulation	>3	3
– No potential to bioaccumulation	<3	0
Eco-toxicity	LC/EC/IC_{50} (fish, daphnia, algae)	
– Low	>100 mg/l	0
– Moderate	10−100 mg/l	1
– High	1−10 mg/l	2
– Very high	<1 mg/l	3

For a particular pharmaceutical substance the scores for persistence, bioaccumulation and eco-toxicity were added. Thus, a substance being easy biodegradable, with no potential to bioaccumulation and a low toxicity, would be given score of 0, while a substance that is not biodegradable, has potential to bioaccumulation and very high toxicity would be given score of 9. It should be noticed that the score interval 0−9 is not linear, for several reasons. First, it is composed of three different variables (i.e. persistence, bioaccumulation and eco-toxicity), which per se cannot be assumed to contribute similar to the total hazard. Second, the variables persistence and bioaccumulation can only adopt the values 0 or 3, while eco-toxicity can adopt all values in the interval 0−3. Third, the mere addition of the variables does not take into account possible synergistic or antagonistic effects between persistence, bioaccumulation and eco-toxicity. Despite these limitations, the system can be considered to provide useful semi-quantitative information.

16.1.2 The Swedish Model for Environmental Classification of Human Medicines

The Swedish Association of the Pharmaceutical Industry (Läkemedelsföreningen, LIF) followed with great interest the emerging interest among the national public health care providers to identify the environmental effects of their products. In response to a conclusion by the national Medical Products Agency (Läkemedelsverket, MPA) that a mandatory system for environmental classification of medicinal substances would be an offence against EU law, LIF invited a number of health care parties in Sweden to establish a national voluntary system.

A working group was established, representing LIF, MPA, ABA, SCC and the Swedish Federation of County Councils. The process in the working group was followed and supported by an international "shadow" group consisting of representatives from the pharmaceutical producers Merck, Lilly, Pfizer, GlaxoSmithKline, Roche and AstraZeneca. In April 2005 the working group presented a proposal for classification based on both risk and hazard. It was explicitly expressed that the system would be refined and adjusted according to (1) experiences obtained during its subsequent use, (2) development of improved methods for testing environmental impact and (3) release of improved data from the producers on their respective substances' metabolism and degradation. The proposal to classification was, after consultation with patient organisations and other stakeholders (governmental authorities, non-governmental organisations, university eco-toxicologists, water authorities), adopted.

According to the new classification system, given the name "the Swedish model" the producers are required to deliver test data on toxicity, persistence and potential to bioaccumulation. Risk for a particular substance is calculated on the basis of composed sales in Sweden from all producers. Risk calculation is performed by the respective producers, and data are presented on the website www.fass.se. All environmental data presented on this site are reviewed and audited by an independent part (Svenska Miljöinstitutet, IVL).

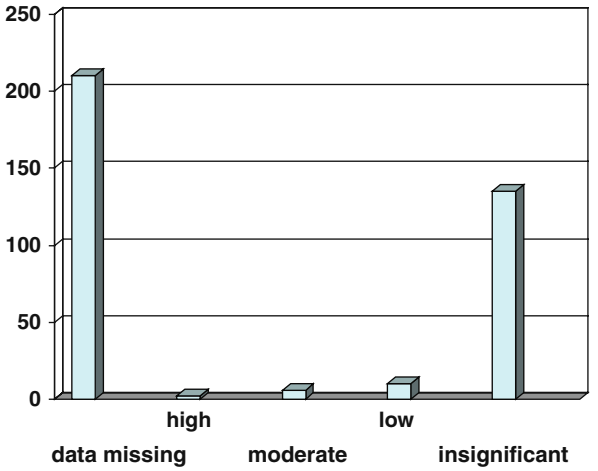


Fig. 16.1 Result of risk assessment of 363 pharmaceutical substances. "Data missing" indicates that the producer was unable to deliver substance data. "High" indicates a PEC/PNEC >10, moderate risk PEC/PNEC ratio 1−10, and low and insignificant risk PEC/PNEC ratio <1 and <0.1, respectively

The first risk and hazard assessments according to the Swedish model were presented in October 2005, including substances belonging to ATC (Anatomical Therapeutic Chemical classification system) groups G (Genito urinary system and sex hormones) and J (Antiinfectives for systemic use). Since then, 2–4 ATC subgroups have been classified annually. It is planned that all ATC groups will be classified by the end of 2010 (Fig. 16.1).

A description of the Swedish model can be found on the website (www.fass.se). Briefly, risk calculation is based on the PEC/PNEC ratio, in which PNEC is the predicted no effect concentration as evaluated on the basis of laboratory experiments in three different trophic levels of aquatic organisms. This use of the PEC/PNEC ratio is mainly in accordance with the EMEA guidelines (EMEA). The resulting ratio is translated to a risk statement:

Use of the substance has been considered to result in insignificant (low/moderate/high) environmental risk

(if the ratio PEC/PNEC is less than 0.1 [between 0.1 and 1/between 1 and 10/higher than 10]). If there is not sufficient data to calculate the PEC/PNEC ratio, either of the following two statements will be used:

Risk of environmental impact cannot be excluded, since no eco-toxicity data are available
Risk of environmental impact cannot be excluded; however some eco-toxicity data are available

Hazard assessment is performed by evaluating the biodegradation and the potential to bioaccumulation of the medicinal substance. Biodegradation is assessed according to standard OECD tests, and yield either of the following phrases on degradability:

The substance is *degraded* in the environment
The substance is *slowly degraded* in the environment
The substance is *potentially* persistent

Also, the potential to bioaccumulation is assessed according to standard OECD tests, yielding either of the following phrases:

No significant bioaccumulation *potential*
Potential to bioaccumulate in aquatic organisms

Some groups of substances are exempted from assessment according to the Swedish model. This is in line with the EMEA guidelines for risk assessment of pharmaceuticals. The exempted groups are vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines and herbal medicinal products.

16.2 Outcome and Experiences of the Risk and Hazard Assessments

ATC groups or subgroups have been reviewed according to a schedule covering 2−4 groups annually. Full compliance to deliver information has been obtained from all agents or producers, but the required data have not always been available, i.e. the agents or producers reported that they lacked the requested information.

By the end of 2009 the ATC groups reviewed will include about 700 of the 1,275 pharmaceutical substances on the Swedish market. These ATC groups cover more than 70% of the defined annual daily doses (DDD) sold. Among the 554 substances reviewed, 191 were exempted from assessment (vitamins, electrolytes, etc., cf above), and in another 210 cases the producers lacked sufficient data for assessment (Fig. 16.1). A total of 153 substances underwent complete risk assessment.

Among these 153 substances, 135 were found to pose *insignificant* environmental risk, and another 10 substances were found to pose *low* environmental risk. Six substances qualified to pose *moderate* risk, and two substances (estradiol and

Table 16.2 Result of hazard assessment in 363 pharmaceutical substances. "Data missing" indicates that the producer was unable to deliver substance data. Hazard was evaluated in terms of the persistence/degradation ("degradable", "slowly degradable" or "potentially persistent") and potential to bioaccumulation of the substance under review

Persistence/degradation				Potential to biodegradation		
Data missing	Degradable	Slowly degradable	Potentially persistent	Data missing	No significant bioaccumulation potential	Potential to bioaccumulation
143	24	121	75	133	189	41

ethinyl estradiol) had a PEC/PNEC ratio >10, thereby qualifying to pose *high* environmental risk.

In the hazard classification, data for evaluation of persistence were available in 220 substances and missing in 143 substances (Table 16.2). Twenty four substances were *degradable*, 121 were *slowly degradable*, and 75 were *potentially persistent*.

Potential to bioaccumulation was possible to evaluate in 230 substances; in 133 cases such data were missing. A total of 189 substances displayed *no significant* bioaccumulation *potential*, while 41 had *potential* to bioaccumulate in aquatic organisms.

16.3 Comments on the Experiences of the Swedish Model

In the present classification system for pharmaceutical products it was an intention to align the system to the principles and test tools already existing for other consumer products of chemical character. Hence the OECD tests for degradability and potential to bioaccumulation were used, as well as eco-toxicity tests using different lethality terms on different trophic level. In the risk assessment the PEC/PNEC ratio was used, mainly as suggested by EMEA in its recent technical guidance document (EMEA). We assume that such alignment to existing evaluation principles and parameters may enhance the acceptance of the system among subscribers and the general public.

The most striking features after some years of using environmental classification of human medicinal products is (1) the extensive lack of environmental data for these products and (2) the large extent to which current human medicines are not ready biodegradable.

Before 1995 there were no specified requirements from the drug authorities in the European Union that pharmaceutical producers have to include environmental data when applying for market authorisation of a new product. After 1995 such data were required, but type, quality and quantity of data were not specified. Not until the new legislation of human medicines became operative in the member countries in late 2005 was more precise documentation called for. The lack of earlier requirements for environmental data obviously made the producers refrain from producing risk assessment studies. With the new legislation, combined with the constant turnover of marketed medicines, it may be assumed that the number of drugs with adequate environmental information will grow.

Risk assessment, using the Swedish model, revealed that 5% of the medicines had a PEC/PNEC ratio above 1, i.e. that the calculated environmental concentration of active ingredient (AI) exceeded the safety level PNEC. Among those AIs, two (estradiol and ethinyl estradiol) had a ratio >10, implying that the safety level was exceeded by a factor 10. The other AIs exceeding ratio 1 were either biodegradable (acetylsalicylic acid and propranolol) or slowly biodegradable/potentially persistent (allopurinol, amoxicillin, raloxiphen and sertralin). An AI which is biodegradable can be considered to pose less risk to the environment than an AI which is slowly biodegradable or potentially persistent, provided that their respective potentials

to bioaccumulation do not differ. Hence, risk assessment only is not sufficient to evaluate the possible environmental impact caused by a medicinal product (or any chemical). A correct assessment should jointly consider both risk and hazard connected to the use of the product.

Hazard assessment was also hampered by lack of data, albeit not to the extent characterising risk assessment. A large proportion – almost 90% – of the AIs were slowly degradable or potentially persistent. This is most likely a reflection of the regulatory requirement that medicinal products should tolerate storage for some years; products stable in the pharmacy shop or in the patients' drug cabinet are also stable in the sewage treatment plants. Potential to bioaccumulation was not a frequent property of the medicines evaluated so far; only about 18% displayed a log K_{OW} value >3.

The producers were initially concerned that some patients would not take medicines which might cause negative environmental effects. No such effects have been observed. The classification has therefore progressively become better received by the producers after a short initial period of some reluctance. It now seems that openness and transparency towards users is a positive factor, yielding credibility and responsibility to the producers.

The prescribers may benefit from the system in different ways. First, all public health care providers in Sweden are enforced by law to establish pharmaceutical committees, whose members should be experienced and well-reputed clinical specialists in various medical areas. The task of these committees is to make selections of medicines to be recommended as first choice in various clinical conditions. In several regions these committees integrate the outcome of the environmental classification in their recommendations as a second priority (medical aspects are always first priority). Thus, when following these recommendations the prescribers also make an environmentally favourable selection. Second, in cases where these recommendations cannot be followed for some reason, the doctor may want to select an environmentally favourable alternative among the conceivable medicines with proper clinical effect. The classification system may then be able to support the doctor in finding such an alternative.

Considerable international interest has been shown towards the Swedish model for environmental classification of pharmaceutical substances, from pharmaceutical companies, from various EU projects, from pharmaceutical authorities and from the various health care providers. In line with this interest it appears reasonable to induce a dialogue with proper EU authorities to reconsider the proposal on a common environmental classification system of pharmaceuticals operative throughout the European Community.

References

EMEA European Medicines Agency. Guideline on the environmental risk assessment of medicinal products for human use.http://www.emea.europa.eu/pdfs/human/swp/444700en.pdf

OECD Test guidelines for testing of chemicals (see http://www.oecd.org/)

http://www.fass.se The website published by the Swedish Association of the pharmaceutical industry

Part V
Incentives, Regulation and the Market

Chapter 17
European Regulations

Eleftheria Kampa, Thomas Dworak, Cornelius Laaser, and Rodrigo Vidaurre

17.1 Introduction

This chapter reviews key existing policy instruments and approaches at EU level that are relevant to limiting the discharge of pharmaceutical products (PPs) into the aquatic environment. EU policies treated in this review address issues of authorisation of PPs, pollution prevention, wastewater treatment as well as monitoring of environmental quality. The analysis serves as a basis for the identification of potential gaps in current approaches. Future policy action might build on this assessment in order to reduce the risk of harmful impacts to the environment.

The chapter starts off with an overview of the EU policy framework relevant to the presence of PPs in the environment. The review puts PPs into the broader context of European environmental protection policies but also pays particular attention to regulations directly relevant to medicinal products. In this context, it seeks to establish links to important water and other natural resource protection policies, such as the EU Water Framework Directive, the Groundwater Directive or the European Soil Strategy. The presentation of EU medicinal regulations, including environmental risk assessment requirements for PPs, is kept concise and refers to the extensive publications of other scholars on this topic. Policies on animal medicine are treated less extensively and only in so far as they are relevant to the water environment.

In the final section, an integrated discussion of the current policy framework is provided, based on the findings of the present review as well as existing expert literature and discussion papers.

17.2 Policy Framework at EU Level

The following outlines the key elements of the EU policy framework, which are relevant to current discussions on the presence of PPs in the aquatic environment. First, the development of regulations for the authorisation of medicinal

E. Kampa (✉)
Ecologic Institute, D-10717 Berlin, Germany
e-mail: eleftheria.kampa@ecologic.eu

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_17, © Springer-Verlag Berlin Heidelberg 2010

products is described; progressively these regulations have given more emphasis to the environmental risk assessment of PPs. Second, the section explores existing and potential links of PPs and current EU policies on environmental and water protection.

17.2.1 Medicinal Regulations and Policies

17.2.1.1 Product Authorisation and Environment Risk Assessment

In the EU, environmental risk assessment (ERA) for pharmaceuticals during product authorisation is currently regulated by Directives 2004/27/EC on human medicine, 2004/28/EC on veterinary medicine and the new regulation EC/726/2004 for medicine containing or consisting of genetically modified organisms. These directives mainly address environmental risk in the consumption phase of PPs. The minimisation of environmental impacts during the production phase of PPs is governed by the EU IPPC Directive 96/61/EC on Integrated Pollution Prevention Control from industrial sources.

According to Directive 2004/27/EC on human PPs, environmental effects must be examined for all new authorisations of PPs and this assessment must accompany the authorisation application. The environmental risk assessment typically involves the generation of data on the environmental exposure and ecotoxicity of PPs. Prior to 2004, detailed environmental risk assessment was only carried out in exceptional cases for human medicine (Holzmann 2005). However, the granting of a marketing authorisation of human medicine cannot be refused using the environmental impact as criterion.

For veterinary PPs regulated under 2004/28/EC, the situation is different. In contrast to human PPs, the granting of a marketing authorisation of a veterinary medicine can be denied due to an unacceptable risk for the environment (Koschorreck and Apel 2006). The 2004 EU regulatory amendments indeed introduced certain key changes in the authorisation of veterinary medicine. The criterion of environmental safety has been given the same weight as consumer safety in the concluding risk-benefit assessment and, therefore, can decide about the authorisation or non-authorisation of a new veterinary PP (Holzmann 2005).

In addition to the legal requirements set in the directives listed above, specific guidelines are available which recommend the scope and the actual procedure for the environmental assessment of medicinal products. Currently, the ERA of human pharmaceuticals is based on the Guidelines of the European Agency for the Evaluation of Medicinal Products (EMEA),[1] while the environmental impact assessment (EIA) of veterinary pharmaceuticals is based on the VICH guidance

[1] Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency. London, 01 June 2006. Doc. Ref. EMEA/CHMP/SWP/4447/00.

(International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products).[2]

The current EMEA guidance document for human medicinal products came into effect at the end of 2006. In fact, first drafts of the guidance have existed since the beginning of the 1990s. Although this early guidance was no regulation nor had it any legal significance, in practice pharmaceutical companies started to orient themselves at these drafts. According to the guidance currently in force, an ERA is required for all new drug marketing authorisation applications as well as for applications requesting major changes or extensions to existing authorisations which would result in an increase in the environment's exposure to the drugs in question. An ERA is not required for renewals of authorisations or applications requesting minor changes to existing marketing authorisations.[3] There may also be cases in which the absence of an ERA could be justified, e.g. marketing authorisation applications for generic medicinal products. Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents. In the case of marketing authorisation applications for radio-pharmaceutical precursors for radio-labelling and radio-pharmaceuticals, additional requirements on emission standards for radiation set by Council Directives 96/29/Euratom and 97/43/Euratom should be taken into account (CHMP 2006).

The ERA follows a two-phased structure of assessment (see Fig. 17.1):

- In Phase I, the drug concentration expected to occur in the aquatic environment is calculated (predicted environmental concentration ($PEC_{surfacewater}$). If the PEC is below a defined action limit of 0.01 μg/l, it is assumed that this specific medicinal product is unlikely to represent a risk for the environment. Thus, the assessment procedure does not continue. If the calculated PEC is equal or above this action limit, a Phase II environmental fate and effects analysis is required. In some cases, the action limit may not be applicable. Some drug substances may affect the reproduction of vertebrate or lower animals at concentrations lower than 0.01 μg/l. These substances have to enter Phase II and a tailored risk assessment strategy must be followed that addresses its specific mechanism of action.

---

[2] Guidance for industry: Environmental Impact Assessment (EIAs) for veterinary medicinal products (VMPs). VICH International Cooperation for on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. Phase I (VICH GL6) and Phase II (VICH GL38).

[3] Minor changes to a drug marketing authorisation are in fact notifications, i.e. applicants just inform regulatory authorities and implement the changes without delay or approval. Examples are change in the name or address of the marketing authorisation holder or the manufacturer, change in the name of the medicinal product, change in the name of the active substance, minor change in the manufacturing process of the active substance, etc. Examples of major changes to a drug marketing authorisation include change in the manufacturing process of the active substance that could affect efficacy, deletions in security information, deletions of contraindications, changes in adverse reactions, etc.

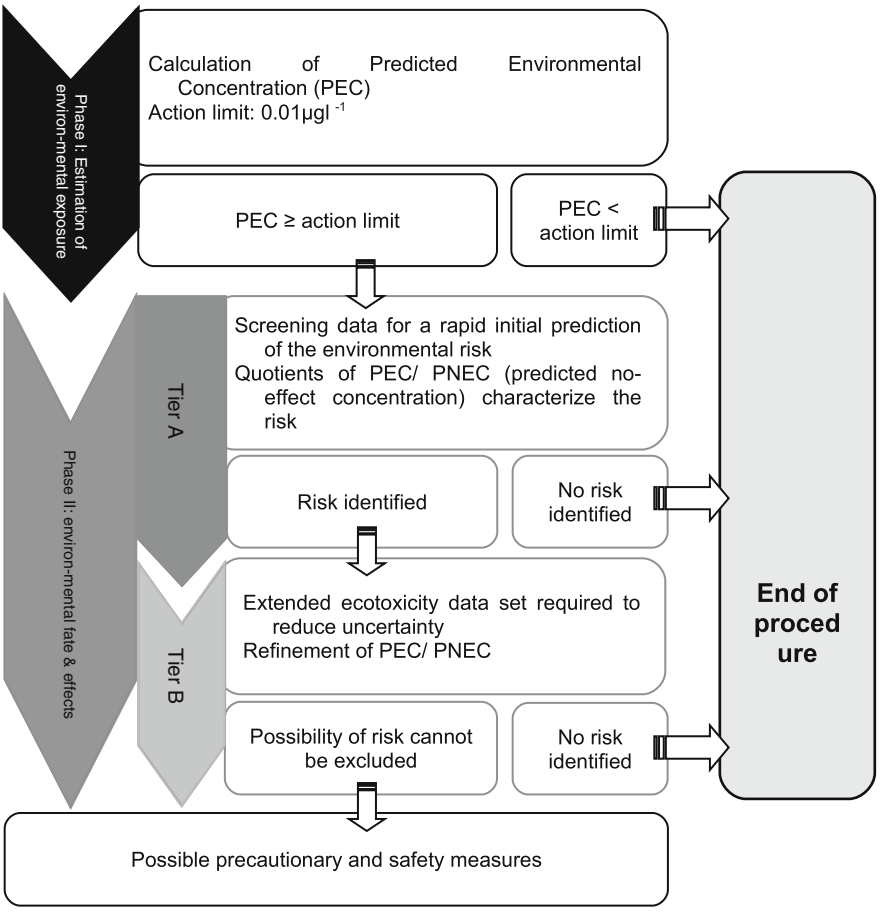


Fig. 17.1 Environmental risk assessment for human pharmaceutical products

- In Phase II, information on the physical, chemical and toxicological properties are obtained and assessed in relation to the extent of the environmental exposure. Phase II is split into Tier A and Tier B. A screening information base set of data for which Tier A is investigated allows for a rapid prediction of the environmental risk linked to the use of the product. Quotients of PEC/PNEC characterise the risk for the aquatic compartment and for microorganisms. PNEC is the predicted no-effect concentration, which is derived from the lowest no observed effect concentration (NOEC) or dose-response result of a set of laboratory ecotoxicity studies representing the aquatic or terrestrial compartment. Certain additional assessment criteria, such as half-life biodegradation, are given with fate data. If at Tier A no risk is identified, the assessment is complete. If at Tier A risk is identified, the subsequent Tier B level requires an extended ecotoxicity data set, which should allow for a reduction of uncertainty and addressing data gaps. Tier

B is the ultimate step in the risk assessment and resembles an iterative process of PEC and PNEC refinement.

As concerns the specific environmental compartments targeted by the ERA for human medicine, it should be noted that in Phase I the PEC calculation is restricted to the aquatic compartment. In Phase II (Tier A), standard long-term toxicity tests on fish, daphnia and algae are carried out to determine the $PNEC_{water}$. An exposure assessment for groundwater is also required, since entry into the groundwater via bank filtration is considered. Furthermore, the fate of the substance in the sewage treatment plant (STP) is investigated via a biodegradability test. The fate of substances which are not readily biodegradable have to be investigated in a water-sediment study. It is assumed that a substance with high adsorption coefficient is retained in the STP and may reach the terrestrial compartment with land spreading of sewage sludge. In this case, an environmental assessment of the drug substance in the terrestrial compartment has to be conducted, unless the substance is readily biodegradable. The terrestrial risk assessment complements the aquatic risk assessment and does not replace it (CHMP 2006).

In general, in Tier B of Phase II, a base set of tests investigating biodegradation in soil, toxicity to soil invertebrates and acute effects on terrestrial plants and microorganisms is conducted. If a substance is not readily biodegradable and if the results from the water-sediment study demonstrate significant shifting of the drug substance to the sediment, effects on sediment organisms have to be investigated (CHMP 2006).

At the end of the ERA procedure, if the possibility of environmental risk cannot be excluded, specific arrangements to limit risk should be envisaged on a case-by-case basis (possible precautionary and safety measures). In any event, in the case of human medicine, environmental impacts cannot constitute a criterion for refusal of a marketing authorisation according to Directive 2004/27/EC.

More details on the ERA process of human medicine can be found in the EMEA 2006 guideline (CHMP 2006) as well as in the literature (Kümmerer 2004, 2008a, Koschorreck and Apel 2006, Umweltbundesamt 2005).

For veterinary medicinal products, first draft EU guidelines on their EIA already existed in the early 1990s. The VICH guideline on Phase I assessment currently in force dates back to 2001 (VICH 2001). In addition, in 2005, the VICH Phase II guidelines came into force in the EU. According to the present guidelines for veterinary medicine, an EIA is mandatory for all new applications, independent of the application procedure (central or national marketing authorisation) and type ("full", "generic" etc.), and is therefore required for all marketing authorisations submitted in the EU irrespective of the underlying legal basis. In respect of renewals, the legal provisions require "a re-evaluation of the risk-benefit balance". Further guidance on the interpretation of the data requirements, in particular in respect of marketing authorisation applications for generics, extensions and variations, as well as for renewals, is under development (CVMP 2007).

The EIA for veterinary medicine follows the same two-phased structure (Phase I and Phase II with Tiers A and B) as the ERA for human medicine (see Fig. 17.1).

However, some key differences exist due to the different nature and areas of application of human and veterinary medicine.

For instance, in Phase I, the EIA for veterinary medicine is distinguished into an aquatic and a terrestrial branch, depending on whether the medicine is used to treat aquatic or terrestrial species. Distinct PECs are thus calculated for soil and water, while ecotoxicity studies are related respectively to aquatic species and terrestrial species (earthworms, microbes and plants). In the aquatic branch, the EIA continues beyond Phase I only if the environmental introduction concentration of the medicine ($EIC_{aquatic}$) is calculated to be more than 1 μg/l. In the terrestrial branch, the EIA continues beyond Phase I only if the predicted environmental concentration of the medicine in the soil (PEC_{soil}) is calculated to be more than 100 μg/kg.

The Phase II guidance for veterinary medicine contains different sections for each of the following major branches: aquaculture, intensively reared terrestrial animals, and pasture animals. Exposure to both the terrestrial and aquatic compartment may be applicable to a particular medicine, depending on its route of environmental introduction. For instance, veterinary medicine administered to intensively reared animals has the potential to impact terrestrial non-target species directly, and non-target species indirectly in surface waters due to transport via water, including when adsorbed to soil particles and organic matter. In this case, due to possible leaching of active ingredients into groundwater, it is necessary to calculate PECs both for surface and groundwater. Veterinary medicine used to treat pasture animals may also impact terrestrial non-target species, as well as non-target species in surface waters. Therefore, also in the case of medicine for pasture animals, it is necessary to calculate PECs for both surface and groundwater.

In general, if there is evidence that there will be no exposure to a particular compartment (i.e. water, soil/sediment and dung), then it may be possible to waive studies for that compartment. However, sound scientific evidence must be presented in the marketing application dossier supporting the omission of these studies.

In the end of the EIA procedure for veterinary medicine, doubts about the acceptability of environmental risk can lead to changes of the characteristics of the product or of the area of application of the product, or even the refusal of marketing authorisation by the authorities.

17.2.1.2 Drug Take-Back Schemes

EU medicinal legislation requires the set up of take-back schemes for unused and expired medicine in all Member States (see Vollmer, Chap. 11, this book). These requirements are set out in Directive 2004/27/EC for human medicinal products (Article 127b). Reference to these collection systems is to be made on the labelling or package leaflet. These systems had to be set up by the end of October 2005. As concerns veterinary products, the requirement to have appropriate collection systems dates back to 2001 and was set out by Directive 2001/82/EC.

Take-back schemes are, on the one hand, a means to reduce the increased presence of pharmaceuticals in the environment. If not disposed of in a sound way, unused and expired medicine can enter the water environment either directly when

flushed down the toilet or indirectly via landfill leachate when disposed of in domestic solid waste (landfill leachate may contaminate groundwater if the landfill is not properly sealed). On the other hand, take-back schemes also target the problem of unsafe pharmaceutical storage practices that can result in accidental poisonings and drug abuse. The extent of the establishment and the degree of effectiveness of take-back schemes for human drugs is quite different among European countries (see Vollmer, Chap. 11, this book). In-depth assessments of scheme effectiveness (estimated recovery rate of unused/expired drugs) are missing for most countries. Individual available assessments often provide different and contradictory figures, pointing to the need for a more consistent approach that should be used in such evaluations. High levels of public awareness and education on the environmental consequences of the disposal of unused/expired drugs seem to be essential for the success of such schemes (Clark et al. 2007).

17.2.2 Environmental Protection Regulations and Policies

The following introduces key EU water policies, but also other EU environmental policies and initiatives which are related or could become related to the issue of PPs in the (aquatic) environment of Europe.

17.2.2.1 Water Policies

Water Framework Directive (WFD)

Directive 2000/60/EC (WFD) requires reaching good status in all EU waters by 2015. For surface water, "good status" is defined as "the status achieved by a surface water body when both its ecological status and its chemical status are at least good". In general, "good status" is defined as "slight changes in the values of the relevant quality elements as compared to the values found at closely undisturbed conditions". The requirement of the WFD for good chemical status of water refers to the concentration of substances that are harmful to the ecosystem.

During production, distribution, use, and through unintentional loss, many chemical substances enter the aquatic environment. Depending on their physico-chemical properties, they can impair the ecosystem and pose a risk to human health. The WFD established two paths to minimize negative impacts of chemical substances on water bodies:

1. *Definition of a list of priority substances* that are considered to be particularly harmful to the aquatic environment on a European scale due to their toxicity, persistence and bioaccumulation potential. Candidate substances for the list were selected on a "list-based" approach, according to which the candidates were

selected from official lists and monitoring programmes.[4] In summary, 658 substances were compiled (Klein et al. 1999). More than 300 of them were subject to risk assessment and extensive consultations before a final list of priority substances was published (Decision 2455/2001/EC), which then became Annex X of the Directive. Annex X of the WFD lists 33 priority substances (mostly organic pollutants (e.g. pesticides), but also some heavy metals and others), for which the European Commission has to define environmental quality standards according to Article 16(7). Member States must apply measures to reduce progressively the concentration of priority substances below the defined quality standards. In case of priority hazardous substances, measures have to aim at cessation or phasing-out of discharges.

At present, no pharmaceutical products are on the list of priority substances, with the exception of a few substances that have a broad spectrum of application and are also being used in the research and/or manufacturing of PPs.[5] The selection process for the first list of priority substances dates back almost 10 years and was based on already existing official lists of pollutants. PPs, however, are often referred to as emerging pollutants, which means that their presence in and impact on the aquatic environment is just being discovered and researched. According to WFD Article 16(4), the European Commission is asked to review the list of priority substances every 4 years. By definition, PPs that could be nominated for the list must exhibit toxic, persistent and eventually bio-accumulative characteristics, and therefore have relevance on a supra-national scale. Moreover, there is still considerable uncertainty regarding the risk of long-term uptake of substances that are presumably not harmful in traces. In this context, the WFD puts emphasis on the precautionary principle, stating that, especially in identifying priority hazardous substances, any potential adverse effects of the product should be taken into account and should lead to a scientific assessment of the risk (recital 11 and 44, WFD).

In recent discussions on the proposed Directive of environmental quality standards amending the WFD,[6] three pharmaceutical substances (carbamazepine, diclofenac and iopamidol) were proposed as "subject to identification as possible priority substances".[7]However, in the final compromise reached between the

[4] List I and II of Council Directive 76/464/EEC, Annex 1A and 1D of the Third North Sea Conference (3. NSC), Priority lists 1−3 identified under Council Regulation No 793/93, OSPAR list of individual candidate substances, HELCOM lists of priority substances, Pesticides prioritised under Council Directive 91/414/EEC, Monitored substances not mentioned on any of the lists above (based on the monitoring data obtained from Member States) (Klein et al. 1999, p. 7).

[5] For example, trichloromethane (chloroform), trichloroethylene, tetrachloromethane, nonylphenol, naphthalene, mercury, dicloromethane, cadmium, chlorobenzene, anthracene, dicloroethane.

[6] COM(2006) 398 final: Proposal for a Directive of the European Parliament and of the Council on environmental quality standards in the field of water policy and amending Directive 2000/60/EC.

[7] European Parliament, Committee on the Environment, Public Health and Food Safety 2007: Compromise Amendments 1−3. Proposal for a Directive of the European Parliament and of the Council on environmental quality standards in the field of water policy and amending Directive

European Parliament and the Council of Ministers, these pharmaceutical substances as well as several other proposed substances were dropped from the finally agreed list of substances to be subject to environmental quality standards under the new Directive 2008/105/EC.[8]

2. *Requirement to identify all other pollutants that are discharged in significant quantities in the river basin or sub-basin*. Member States have to set quality standards for such river basin-specific pollutants, and take action to meet those quality standards by 2015 as part of good ecological status (Article 4, 11 and Annex V, WFD). This refers predominantly to substances listed in Annex VIII of the WFD which provides an indicative list of the main pollutants and inter alia covers *substances and preparations, or the breakdown products of such, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect steroidogenic, thyroid, reproduction or other endocrine-related functions in or via the aquatic environment.* (Annex VIII, No.4, WFD).

   If PPs that enter the aquatic environment in significant quantities pose a risk to a water body due to their physico-chemical properties, they have to be covered by this requirement. The prioritisation to identify Annex VIII substances is an ongoing process, with the possibility of further substances being added (and their corresponding standards for environmental quality proposed). The process uses criteria on occurrence, persistence, toxicity and bioaccumulation in order to identify new substances. Oestradiol and ethinyl oestradiol have both been identified by the Environment Agency as *potential* UK specific pollutants. At the time of writing, work was under way to investigate whether PNECs (predicted no effect concentrations) can be developed for these substances. Based on the outcomes of this work and peer reviews, these substances may or may not become UK specific pollutants (Environment Agency UK, January 2008, personal communication).

Consistently implemented, the two above-mentioned paths of the WFD provide the means to track down and minimise the effects of harmful chemical substances discharged into the aquatic environment. However, it should be mentioned that the comprehensive WFD mechanisms for maintaining and improving the overall quality of all waters in Europe can only work if the pressure on the aquatic environment and the related risk have been detected. Regarding pharmaceuticals, this process is currently only beginning and is being complicated by the fact that the presence of pharmaceutical products is in many cases difficult to detect with existing standard analytical methods. On the other hand, one of the strengths of the WFD is that its implementation (identifying pressures and impacts on water bodies, design of monitoring programmes, developing river basin management plans) is designed

---

2000/60/EC. Draft report (PE 378.719v01-00), Anne Laperrouze. PE 386.558v01-00. 26.3.2007. http://www.europarl.europa.eu/meetdocs/2004_2009/documents/dv/659/659305/659305en.pdf

[8] Directive 2008/105/EC on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC.

as an iterative process, and new findings can thus be included in the next management cycle. PPs can be incorporated into this scheme, once more data have become available.

Furthermore, most Member States are currently adjusting their water monitoring programmes to the main pollutants[9] (e.g. nutrients, heavy metals) and to the requirements set out in the list of priority substances. PPs are mostly not yet on the agenda when designing monitoring programmes. However, in countries like UK, Germany and several Swedish counties, monitoring of PPs is taking place to some extent within investigation programmes of the authorities on the occurrence and risk of PPs in the environment. In Germany, several pharmaceutically active substances have been checked for inclusion into the WFD assessment of ecological status. Discussions are ongoing on their relevance and possible incorporation into the list of chemical quality standards according to the procedure outlined in Annex V 1.2.6 of the WFD (pers. comm., German Federal Environment Agency, August 2009).

Drinking Water Directive

The Drinking Water Directive (DWD) 98/83/EC aims at the protection of human health from harmful influences that might occur through pollution of water intended for human consumption. It also aims at assuring the suitability and purity of water for human consumption. It is strongly linked and synchronised with the WFD. The parameters to be monitored are defined in Article 5 and Annex I of the DWD. It lists 48 parameters (50 for bottled waters) categorised into three distinct groups: microbiological, chemical (meaningful to human health) and indicator parameters (meaningful to supply engineering, aesthetics and health care). No pharmaceutical products are listed in the DWD. However, some substances used in pharmaceutical manufacturing are included in its list (which also appear in the WFD list of priority substances, see above).

In 2003, the European Commission decided not to include endocrine disrupters in the DWD, due to the lack of sensitive detection methods and reliable data concerning their risk to human health in view of their occurrence in water. However, Member States are free to set values for additional parameters not included in Annex I of the DWD, when necessary for the protection of human health. In practice, despite the lack of legal requirements to monitor PPs regularly so far, research projects frequently address the issue of PP concentrations in drinking water.

Groundwater Directive

The new Groundwater Directive 2006/118/EC complements the WFD in terms of chemical status criteria for groundwater. It clarifies good chemical status criteria and specifies how to identify and reverse pollution trends. The Directive establishes

[9] "Main" in terms of amount introduced to the aquatic environment.

a regime which sets groundwater quality standards for a minimum list of pollutants and introduces measures to prevent or limit inputs of pollutants into groundwater. It requires Member States to establish groundwater quality standards by the end of 2008 and publish them in the WFD Programmes of Measures by the end of 2009; in addition, it requires Member States to carry out pollution trend studies using existing data and data which are mandatory by the WFD ("baseline level" data obtained in 2007−2008), to reverse pollution trends so that environmental objectives are achieved by 2015 using the measures set out in the WFD, to make operational measures to prevent or limit inputs of pollutants into groundwater so that WFD environmental objectives can be achieved by 2015 and to comply with good chemical status criteria (based on EU standards of nitrates and pesticides and on threshold values established by Member States).

No pharmaceutical products are listed in the Annexes of the Groundwater Directive. However, Member States are required to "amend the list of threshold values whenever new information on pollutants, groups of pollutants, or indicators of pollution indicates that a threshold value should be set for an additional substance" (Article 3(6), Groundwater Directive). The Directive also includes the requirement to identify and reverse significant increasing trends in pollutant concentrations. The repeated review of the status, trends and measures that is synchronised with the WFD cycles is meant to take new pollutants and risks into account and tackle them accordingly.

Bathing Water Directive

The Bathing Water Directive 2006/7/EC is concerned with monitoring and testing bathing water quality in order to protect bathers from health risks and to preserve the environment from pollution. While the first Directive introduced in 1976 required regular monitoring of 19 pollutants or other parameters (for instance water colour), the revised Directive 2006/7/EC reduces this list to just two microbiological indicators of faecal contamination, *Escherichia coli* and intestinal enterococci. This simplification reflects the fact that, due to most other water pollution being covered by the WFD, the primary health threat to bathers comes from faecal material. The issue of pharmaceuticals in the aquatic environment is therefore not dealt with under this Directive.

Urban Waste Water Treatment Directive

The Urban Waste Water Treatment Directive (UWWTD) 91/271/EEC concerns the collection, treatment and discharge of urban waste water from urban agglomerations. Its purpose is to stimulate Member States to invest in the collection and treatment of urban waste water; the aim is to reduce the input of organic matter and nutrients into European waters according to specific standards and deadlines set out in the Directive (Kemp 2002).

The Directive defines three levels of treatment: primary, secondary and tertiary treatment. The basic rule for the level of treatment is secondary (i.e. biological)

treatment. Treatment has to be more stringent (tertiary with additional nutrient removal) for discharges in so-called sensitive areas (defined according to UWWTD Annex II).

Although the parameters that the UWWTD aims to reduce are only related to organic material and nutrients, a side-effect of treatment is that a large number of other pollutants are also removed from wastewater, in particular many micropollutants such as heavy metals and pharmaceuticals. The reduction of the concentration of pharmaceuticals in treated wastewater depends on the particular treatment processes applied, and increases with higher levels of treatment. However, because many pharmaceuticals resist biodegradation (ICON Consultants 2001), they are frequently found in significant concentrations in sewage sludge.

The UWWTD works with an Emissions Limit Value approach for the parameters it takes into consideration, which can be explicitly subject to changes; it is in theory possible that the Emission Limit Values are extended to other parameters, e.g. pharmaceuticals. However, no other contaminants have been taken up in the Directive's annexes since its adoption. In the same time, the ongoing implementation of the EU WFD poses new challenges to treatment plant operators. Especially the issue of how the treatment plants used to an Emissions Limit Value approach will respond to the WFD approach of Environmental Quality Standards is receiving more and more attention.

17.2.2.2 Other Environmental Policies and Initiatives

European Strategy for Soil Protection

The status of soil is one of the factors regulating water quality; thus, current European policies for soil protection are relevant to water status and possibly also to the presence of pharmaceutical products in environmental waters. In 2006, the European Commission adopted a Communication for a Soil Thematic Strategy and a proposal for a Soil Framework Directive, with the aim of protecting soils across the EU. The Communication for a Soil Thematic Strategy explains why further action is needed to ensure a high level of soil protection, setting the overall objective of the Strategy, and explains what kind of measures must be taken. The proposal for a Framework Directive sets out common principles for protecting soils across the EU, including among others prevention, inventory and remediation of contaminated soil. Although pharmaceutical substances are not part of the current EU policy documents under discussion on soil protection, they have been identified as a priority issue for further research by the working groups set up in preparation of the Soil Strategy (Van-Camp et al. 2004).

Sludge Directive

Sewage sludge used in agriculture is covered by the Sewage Sludge Directive 86/278/EEC. The Directive's aim is to "encourage the correct use of sewage sludge" in agriculture, while preventing "harmful effects on soil, vegetation, animals

and man"; these effects could be due to the uptake of contaminants in agricultural products. The restrictions on the use of sewage sludge are currently limited to seven heavy metals: cadmium, copper, nickel, lead, zinc, mercury and chromium.

The Directive does not make explicit mention of pharmaceuticals in sewage sludge. Because the Directive encourages the application of sewage sludge due to its valuable properties, instead of favouring other forms of disposal such as combustion, it actually encourages at present the spreading of pharmaceuticals and their residues in the environment. Pharmaceuticals in sewage sludge applied to fields can also end up being leached into groundwater, eventually making their way into surface water and/or drinking water. However, the Directive does foresee a process of its own adaptation to technical and scientific progress, so future changes to the Directive could in theory address pharmaceuticals.

Some German federal States (e.g. Bavaria[10] and Nordrhein-Westphalia[11]) have recently passed legislation and/or programmes that aim to reduce the use of sewage sludge in agriculture. The presence of pharmaceuticals in sewage sludge, and as consequence the possibility of them entering environmental waters, was one of the reasons for taking such decisions.

Endocrine Strategy

Some chemicals can act on the endocrine system to disturb the physiological function of the body or to initiate processes at abnormal times in the life cycle. These so-called endocrine disrupters comprise natural hormones, natural chemicals, man-made chemicals and pharmaceuticals. Indeed, several pharmaceuticals are designed to be hormonally highly active, e.g. the contraceptive pill and treatments for hormone-responsive cancers. The residues of such pharmaceuticals enter the aquatic environment via various pathways and may have endocrine disruption effects on humans and wildlife if taken up unintentionally.

The European Endocrine Strategy addresses the potential environmental and health impacts of endocrine disruption in short-term, mid-term and long-term actions. A key activity within the Strategy is the identification and evaluation of relevant substances for their role in endocrine disruption. Any pharmaceuticals detected to pose risk to consumers under the Endocrine Strategy efforts will be dealt with within existing environmental regulation as far as possible. For the aquatic environment, the Endocrine Strategy refers explicitly to the WFD and its anti-pollution approach (CEC 2004).

---

[10] Bavaria has included as an aim in its waste management plan and in its development programme to abandon the use of sewage sludge in agriculture (cf. speech of State Secretary Dr. Otmar Bernhard at the international symposium on sewage sludge in June 2008, http://www.stmugv.bayern.de/aktuell/reden/detailansicht.htm?tid=14883)

[11] Nordrhein-Westphalen aims to increase the amount of sewage sludge disposed of thermally, cf. Europäischer Wirtschaftsdienst Wasser und Abwasser, Nr. 11, 11.03.2008.

REACH

The REACH Regulation EC No. 1907/2006 deals with the registration, evaluation, authorization and restriction of chemicals. It entered into force on June 1, 2007. It exempts substances "used in" medicinal products from its main provisions, because medicinal products are already regulated within the scope of the Human Use Directive 2001/83, the Veterinary Use Directive 2001/82 and the Regulation 726/2004 (governing the centralized procedure of authorisation and supervision of medicinal products). Some provisions of the Regulation, however, remain applicable, including disclosure of information (on hazardous properties and regarding risk management measures) and restrictions on marketing and use of substances that pose an "unacceptable" health or environmental risk (which will probably rarely be applied to medicinal products) (Bogaert et al. 2007).

IPPC Directive

The IPPC Directive 96/61/EC (on Integrated Pollution Prevention and Control) concerns the minimisation of pollution from various industrial sources. Annex I of the Directive lists industrial installations for which operators are required to obtain an authorisation (environmental permit) from the authorities in the EU countries. The list of installations which have to comply with the terms of the Directive includes "installations using a chemical or biological process for the production of basic pharmaceutical products". New installations of this kind have to apply for a permit and have to show by evidence that emissions to the environment during production are minimal and accord to Best Available Techniques. Furthermore, Annex III lists main polluting substances which should be taken into account for fixing emission limit values. For water, this Annex lists inter alia substances and preparations which have been proved to possess carcinogenic or mutagenic properties or properties which may affect reproduction in or via the aquatic environment as well as persistent hydrocarbons and persistent and bioaccumulable organic toxic substances.

With the above requirements, the IPPC Directive ensures that emission of PPs into the environment during their production process is minimised. All in all, in Europe, there has been much progress in reducing emissions of PPs in the production phase by respecting relevant legislation and by improving the technologies used in industrial manufacturing. It is thus argued that efforts to limit further the discharge of PPs into the environment should concentrate on steps after but also prior to production (design, consumption and disposal phases).

17.3 Discussion of Current Policy Instruments

In this section, the current policy framework and its instruments to limit the discharge of pharmaceutical products (PPs) is discussed, in view of its relevance for the protection of the aquatic environment.

In general, environmental policy responses to water pollution are, as a rule, based on certain principles: the precautionary principle, the principle that pollution

should be avoided at source, the prevention principle as well as the polluter-pays principle.

Current EU policies related to risk reduction from the presence of PPs in the environment can be seen in the context of the precautionary and prevention principles, but also in the context of end-of-pipe solutions (mainly wastewater treatment aspects). Having said that, it should be kept in mind that, in current EU environmental policy, precautionary and preventive approaches instead of end-of-pipe solutions are being promoted at all decision and policy levels.

17.3.1 Policy Framework in the Light of the Precautionary and Prevention Principles

The precautionary principle emphasises that, where evidence of a threat to the health of the environment exists, scientific uncertainty must not be allowed to delay reasonable forms of management action. Therefore, given that concerns exist that pharmaceuticals in natural waters could have subtle, long-term effects on the reproduction, development, and/or behaviour of aquatic species, uncertainty should not be a reason to allow environmental contamination by pharmaceuticals to continue unabated. This urges the scientific and policy community to consider and possibly to implement management strategies to mitigate the release of PPs to the environment (Doerr-MacEwen and Haight 2006).

On the other hand, there are arguments that the interpretation and possible application of the precautionary principle need to be adapted to the conditions of pharmaceutical risk management. The precautionary principle has evolved in the setting of environmental policy making, a field with significant differences to the characteristics of pharmaceutical risk management (Callréus 2005). In a recent review of expert stakeholders' views on the management of pharmaceuticals in the environment, concerns were expressed about the precautionary principle. These concerns were related mainly to the proportionality of management action, the balancing of risks and socioeconomic considerations and the level of scientific evidence required to engage in precautionary management action. Despite concerns, however, a number of risk management strategies for PPs in the environment such as drug take-back schemes, which are required by the EU by Directive 2004/27/EC for human medicinal products (Article 127b) (see Castensson and Ekedahl, Chap. 12, this book; Niquille and Bugnon 2008), were considered by most as sensible approaches (Doerr-MacEwen and Haight 2006).

All in all, environmental concerns are now more strongly integrated in EU regulations on PPs than in the past, at least with respect to the marketing authorisation of PPs. As already mentioned, since September 2005 each new human medicine must undergo environmental risk assessment, while in the case of veterinary medicine authorisation, environmental safety has gained the same weight as consumer safety in the risk-benefit analysis. Also, detailed guidelines are now available for the environmental risk assessment procedure of both human and veterinary medicine.

Nevertheless, certain gaps still exist in the medicinal policy framework, especially in the practical aspects of its implementation; these should be targeted in

future efforts addressing the presence of PPs in the environment. In this context, the authors would like to emphasise the following issues:

- *Environmental safety of "old medicine"*. So far, environmental risk is not assessed for so-called "old medicine". "Old medicine" includes products authorised before the adoption of EU legislation requesting environmental risk assessment (in 1993 for human PPs and in 1990 for veterinary PPs) and the adoption of relevant ERA guidelines (in 2006 for human PPs and in 1998 for veterinary PPs). "Old medicine" indeed constitutes a large proportion of medicinal products authorised and available on the market, and there is currently no system for their environmental evaluation and control. It is argued that, in analogy to similar European regulatory provisions for other groups of substances like industrial chemicals, biocides and pesticides, the environmental safety of "old medicine" (both human and veterinary) should also be assessed. Priority lists for an "old medicine" programme should be drafted, and applied at the European level to minimise the environmental evaluation work load (SRU 2007).
- *Authorisation of veterinary medicine and risk mitigation.* Doubts about the acceptability of the environmental impact of veterinary medicine can lead to changes of the characteristics of the product, of the area of its application or even to the refusal of marketing authorisation by the authorities. An identified environmental impact may also be mitigated to an acceptable level by special precautions included in the information that accompanies the product in labeling and packaging. Such precautions can include, for example, the application of manure coming from treated animals at a minimum distance from surface waters or restrictions to the direct access of treated animals to surface waters. Those addressed by such precautionary measures are livestock owners and those responsible for handling manure. Montforts (2005), however, identified several constraints which decrease the technical and legal effectiveness of such measures. On the one hand, measures taken on the basis of the relevant medicinal Directive (2001/82/EC) are not legally binding for veterinary doctors and farmers (the consumers). Therefore, there seems to be a need for complementary regulations with regard to PP application instructions and their addressees in national legislation in a Europe-wide harmonised manner. On the other hand, precautionary measures are only acceptable under the medicinal Directive 2001/82/EC, if their effect can be demonstrated using risk assessment methodologies. For measures completely prohibiting the release of treated animals or the use of contaminated manure, it is quite easy to demonstrate that they have an effect. However, the impact of temporary storage of contaminated manure or of keeping a security distance of treated animals from surface waters cannot be easily quantified due to the lack of standardised methods. Therefore, to render these precautionary measures effective for risk mitigation (and hence suitable for labelling and packaging), risk assessment methodologies must be further developed and applied.
- *Authorisation of human medicine and risk mitigation.* Although approval of authorisation for veterinary medicine can be refused on the basis of risks to the environment, this is not the case for human medicine. The principle therein is

that the therapeutic benefit for sick humans is to be considered beyond possible damage to the environment. This principle can doubtless be followed; however, a possible future approach could for instance require that the therapeutic benefit be superior to any alternatives and that a broad, little-controllable application (e.g. by recipe-free circulation for self-medication) of pharmaceuticals that pose an environmental risk be prevented. Thus, although it is unrealistic to prohibit the authorisation of human PPs on environmental grounds, different alternatives should be considered in the authorisation process to reduce environmental exposure as far as possible (SRU 2007). If alternative compounds are available promising the same success in therapy, but posing at the same time a lower environmental risk, a refusal of authorisation should not be excluded per se (Knacker et al. 2006). It should also be mentioned that, in general, only little experience for human medicine in the risk management area has been gathered so far (Koschorreck and Apel 2006). In Germany, although the federal environment agency has been successful in a significant number of cases in combining authorisation of veterinary drugs with practicable environmental risk mitigation measures, in the field of human pharmaceuticals there is a need for further practical efforts (Holzmann 2005, Schlimm 2005). At the moment, there is no concrete proposal and no binding regulations for mitigation measures relevant to human medicine (SRU 2007). It is however expected that the 2006 publication of the EMEA guideline on the ERA of human PPs will contribute to the broader use of risk mitigation measures for human PPs.

- *Drug take-back schemes.* The extent of establishment and the degree of effectiveness of take-back schemes for drugs is quite different among European countries (see Vollmer, Chap. 11, this book). In-depth assessments of scheme effectiveness (estimated recovery rate of unused/expired drugs) are missing to a great extent. High levels of public awareness and education, first regarding the environmental consequences of the disposal of unused/expired drugs and, second, on the operation of such schemes, seem to be key for their success. Problems in the implementation of take-back schemes are largely related to lack of awareness, leading to erroneous consumer behaviour. There is thus need to improve the labelling of pharmaceuticals and consumer information, so as to assure the return of unused pharmaceuticals to pharmacies.

As far as the EU policy framework beyond medicinal regulations is concerned, at present it does not adequately take account of the precautionary and prevention principles on the issue of pharmaceuticals in the environment; this is partly due to implementation deficiencies and partly due to legislation gaps. All in all, it is not argued here that additional directives are needed. A suitable EU policy framework seems to be in place already, but some modifications to existing directives may be needed:

- *Water Framework Directive.* The WFD provides an appropriate policy framework to deal with all sources of chemical pollution in European waters if implemented properly.

First, it establishes a list of priority chemical substances for which measures must be progressively applied to reduce their concentration below defined quality standards. It is argued that in future revisions of the list of priority substances, certain PPs should be considered.

Second, the WFD (Annex VIII) requires all other pollutants to be identified that are discharged in significant quantities in the river basins and relevant quality standards to be set that should be met by 2015 as part of good ecological status. The definition of target substances and standards is up to the Member States and to specific basin authorities. For instance, in the UK, two PPs are under discussion for addition to the list of UK specific pollutants according to WFD Annex VIII.

However, all in all, the respective WFD mechanisms and the Directive's precautionary principle are not yet used fully to deal in a focused way with the issue of PPs in the aquatic environment. The issue is currently not politically discussed, which is partly due to its complexity, uncertainties, and lack of knowledge (as described in the next section).

A first important step in order to use better the WFD implementation process for filling in knowledge gaps on PPs in the aquatic environment is to include, where considered necessary, PPs in the "characterisation of river basin districts and review of environmental impact of human activity" (WFD Art. 5). On the basis of "river basin district characterisation" results, decisions for future monitoring of substances and relevant necessary water management measures can be taken.

Appropriate and adequate monitoring of pharmaceutical substances in the environment is in general missing. It is recommended to include the monitoring of specific pharmaceutical substances – those which are of high environmental relevance due to the effects, persistence or mobility – in existing monitoring programmes like those for the WFD implementation (SRU 2007).

- *Drinking Water and Groundwater Directives.* PPs are not listed yet in the Annexes of these two key water directives that refer to substances to be monitored. Nevertheless, with respect to drinking water (whose source is often groundwater), there is frequently concern on possible health impacts due to the presence of PPs. First, public demand for drinking water of good quality cannot be overlooked by water managers. Second, the precautionary principle is often called for in this case, when bearing in mind uncertainties such as the following: the increasing spread of antibiotic-resistant bacteria can pose a health risk for humans; there is lack of knowledge on risk to human health (via drinking water) from chronic exposure to PPs that are designed for short-term use.
- *Bathing Water Directive.* The recent amendment of the Bathing Water Directive may be seen as a step forward when discussing this Directive in the overall framework of new EU water policies. However, due to several implementation gaps of the overall framework and especially the fact that PPs are currently not widely discussed in WFD implementation, there is the risk that the issue of PPs in bathing waters will not receive adequate attention in policy implementation.

- *Other environmental policies and initiatives.* The following refers to the European soil policy, the Sewage Sludge Directive, the EU Endocrine Strategy, the REACH Regulation, and the IPPC Directive:

  – PPs are not yet part of current policy documents under discussion on *European soil protection*. However, the possible relevance of European soil protection for PPs has been identified on a policy level by placing these substances among the priority issues for further research in this field (in terms of their quantification and risk evaluation methods).
  – Despite the fact that PPs' presence in sewage sludge could lead to the unintended uptake of relatively high concentrations of PPs via food consumption (when food is grown on fields where sewage sludge is applied), there are no limits for PP concentrations yet in the *Sewage Sludge Directive*. Another possible fate for pharmaceuticals and other pollutants contained in sewage sludge is their leaching into groundwater, and eventually making their way into surface water and/or drinking water. In fact, in some EU countries, due to preoccupation with the issue of contaminants in sludge, including drugs, the application of sewage sludge on agricultural fields has been prohibited.
  – An identification and evaluation process of substances with potential environmental and health impacts of endocrine disruption continues and improves in the context of the *Endocrine Strategy*. Any pharmaceuticals detected under the Endocrine Strategy efforts will be dealt with in existing environmental regulation as far as possible. For the aquatic environment, the Endocrine Strategy also refers to the WFD and its strategy against pollution.
  – PPs are also exempt from the main provisions on registration, evaluation, authorization, and downstream use of chemicals in the EU *REACH Regulation*. Some provisions of REACH remain applicable, including disclosure of information (on hazardous properties and regarding risk management measures) and restrictions on marketing and use of substances that pose an "unacceptable" health or environmental risk. However, these provisions will probably rarely be applied to medicinal products.
  – The *IPPC Directive*, which aims at pollution prevention and control in industrial production processes, only applies to the production of PPs. This Directive ensures that emission of PPs into the environment during production is minimised. There has been much progress in reducing emissions of PPs in the production phase by respecting relevant legislation and by improving the technologies used in industrial manufacturing. In consequence, efforts to limit further the discharge of PPs into the environment should concentrate on steps beyond (but also prior to) production.

17.3.2 Policy Framework and End-of-Pipe Solutions

Once PPs are released by consumers into sewage, either via urine or after disposal of unused/expired drugs down the drain, only an end-of-pipe solution remains to limit the presence of PPs in the natural aquatic environment.

Although precautionary and pollution preventive policy approaches should be a priority, the policy framework could also be improved in terms of PP removal in the phase of wastewater treatment. The most relevant EU policy is the Urban Wastewater Treatment Directive (UWWTD) which focuses on the reduction of organic material and nutrients. The removal of other pollutants, including pharmaceuticals and heavy metals, has so far only been a side-effect of wastewater treatment.

First, the full implementation of this Directive in all EU Member States would have positive impacts on the levels of occurrence of PPs in the water environment. Second, a future amendment of the UWWTD could be envisioned to include emission limits on pharmaceuticals. Requirements to deal with pharmaceutical loads in wastewater may also result for plant operators from the WFD. Given the new approach of the WFD on water quality, that combines emission limit values with environmental water quality standards, operators of urban wastewater treatment plants may be forced to upgrade their technologies. In any event, technologies which could improve the degree of removal of PPs from wastewater, like ozonation and membrane filtration, are already available. However, such technologies are also under discussion concerning their efficiency and possible environmental impact side-effects, e.g. increased energy demand and unwanted by-products (see, for example, Kümmerer 2008b).

The wastewater treatment policy framework could also be modified to intensify efforts for installing special (pre-)treatment facilities for hospital wastewater, if and where this is assessed to be a good management option. In some countries, hospitals are considered hotspots for pharmaceuticals emissions because their emission route accounts for a high percentage of the total load of human pharmaceuticals in the environment (e.g. see Roorda et al. 2008 for an illustration of the situation in the Netherlands). However, in other countries, this is not the case (see, for example, Kümmerer and Schuster 2008). Thus, although hospitals may be in certain cases hotspots for pharmaceutical emissions, their contribution to total loads of pharmaceuticals is low and therefore their separate treatment at the hospital should be at least questionable. Certainly, a detailed analysis for selecting the most cost-effective alternative (municipal treatment and/or on-site hospital treatment) should be made for each specific case or on national level (see Wenzel et al. 2008, Jones et al. 2007).

In this entire discussion on wastewater treatment options, a crucial issue is the cost recovery for investments in new technologies. Next to possible policy modifications, economic instruments (e.g. ear-marked water taxes) could be used to support financially the upgrade of treatment. In this context, it is important to clarify the role of the polluter (industry or consumer) in order to develop an appropriate approach for implementing the polluter-pays principle.

17.3.3 What Complicates Further EU Policy Development to Limit Discharge of PPs into Waters?

Based on the discussions above, it is apparent that there are still certain policy gaps (either legislative gaps or gaps in the implementation of legislation) when it comes

to the issue of PPs in the aquatic environment. Taking further action to close some of these gaps is, however, still difficult, due to lack of relevant information and knowledge as well as uncertainties on PPs in the environment.

It becomes clear that we need *better understanding, better data and further research* on PPs in the aquatic environment. Some of the key issues to be clarified include:

- *Knowledge on the fate and effects of PPs in the environment.* So far, knowledge on the fate and effects of PPs in the environment has been sparse. It is hoped, however, that, given the recent adoption of EU guidelines on the ERA of PPs, more data on the fate and effects of PPs will be generated in the near future (Koschorreck and Apel 2006).
- *Knowledge on low-level effects and chronic effects of PPs.* The environmental risk assessment for PPs should guarantee that possible low level and long-term effects of PPs are not overlooked. The strict application of an action limit, which terminates any further risk assessment for substances not exceeding the PEC in surface water (0.01 μg/l for human medicine), may lead to the disregarding of such effects, considering that experience with the ecotoxicological effects of human PPs is still very limited.

  Concerning chronic effects, more data need to be made available that allow their assessment in ecotoxicological studies, especially for products that have been on the market for a long time.

  Concerning low-level effects, there is a strong opinion that pharmaceutical compounds do not pose a large risk because they are present in such low concentrations (ng/L), with most effects only seen in the mg/L range. However, it should be kept in mind that disease resistance to pharmaceuticals is favoured by low concentration exposure and compounds such as hormones have effects at very low levels. The effects of active compounds in the low (ng/L) range cannot be excluded; as experience with pesticides has shown, impacts can be significant at low levels (Stuer-Lauridsen et al. 2000).
- *Cumulative effects of multiple PP substances.* Although in the environment organisms are exposed to a variety of substances, the potential impact of mixtures of individual substances in the environment is recognised as an unresolved issue within the currently implemented ERA schemes. Especially in the case of pharmaceuticals from similar medicinal classes, it can be expected that they have similar modes of action under environmental conditions, and hence, additive or synergistic effects are likely to occur (Knacker et al. 2006). So far, only individual products undergo an environmental risk assessment and thus the risk assessment process is lacking in cumulative assessments of potential environmental risk from substances of comparable structure (SRU 2007).
- *General data availability and accessibility.* At present, the limited quality of data used in ERA and the difficulty to access ERA information used in marketing authorisations remain key problems for several interested stakeholders. There is also great unbalance on data availability for newly authorised PPs vs PPs brought on the market prior to ERA regulations (SRU 2007). In addition, ERA data and information are only open to the respective national competent

authorities (with the exception of Sweden where ERA results are made public online on a voluntary basis). The UK Environment Agency argues for open access to non-commercially sensitive information to facilitate effective environmental assessments. It has thus called upon the EMEA and the MHRA (the English equivalent) to put in place a suitable system making environmental information on pharmaceuticals easily available and accessible (Environment Agency 2003).

Another important data limitation concerns figures for medication consumption. In most countries, and for both human and veterinary products, no reliable figures for pharmaceutical use are available. This is an important stumbling block when trying to determine the environmental impacts of the use of human and veterinary pharmaceuticals. A possible way of addressing this issue is to increase the requirements regarding the documentation of use (SRU 2007).

Besides the scientific and data gaps highlighted above, the following issue further complicates policy discussions on PPs in the environment. Namely, difficulties in setting regulatory limits on the release of PPs into water from different sources (the public, wastewater treatment plants, industry) and in applying economic instruments (e.g. taxes to finance pollution-reduction measures and the "polluter-pays-principle") result from the question "who is the polluter". Different definitions of the polluter (consumers of medicine; industry; doctors as prescribers; hospitals; pharmacists; or even public agencies issuing PP marketing authorisations) can be used, with varying implications. It is thus important to clarify who the polluter is and to carry out research on the costs and benefits of the different options.

All in all, the development of policy options and instruments to limit the discharge of PPs into the aquatic environment certainly requires an open consultation and dialogue process involving key public and private stakeholders. The need to amend existing policies or to develop new policies has to be based on a balanced consideration of the precautionary and prevention principles of environmental policy making, the polluter-pays principle as well as new scientific knowledge on the risks and impacts of the unintended release of PPs into water.

Finally, it should be kept in mind that the pool of optional approaches to limit the discharge of PPs into the aquatic environment goes also beyond EU regulations and policies. In this context, the following actors can play a role in various ways: the industry (e.g. by better communication of the environmental risk of drugs via environmental classification systems or by introducing environmental criteria in the early steps of product development), the public domain (e.g. by promoting and ensuring safe waste disposal with incineration), the health care system, doctors as well as patients (e.g. by responding to communication efforts on the environmental risk of PPs and making better use of drug take-back schemes).

Acknowledgments The authors gratefully acknowledge financial support from DG Research of the European Commission under the Sixth Framework Programme for Research, Technological Development and Demonstration Activities for the Specific Support Action "KNAPPE" (Contract No. 036864).

References

Bogaert P, Kingham R, Castle G, Molyneux CG (2007) REACH and its impact on pharmaceuticals. Covington E-Alert, Covington & Burling LLP. http://www.cov.com/files/Publication/ed03bc97-89de-471d-9163-4f1a26899ba2/Presentation/PublicationAttachment/e60742d7-e808-45a9-bec6-590676c12a9a/735.pdf

Callréus T (2005) The precautionary principle and pharmaceutical risk management. Drug Saf 28, 465−471

CEC – Commission of the European Communities (2004) Commission Staff Working Document on implementation of the Community Strategy for Endocrine Disrupters – a range of substances suspected of interfering with the hormone systems of humans and wildlife. COM (1999) 706

CHMP – Committee for Medicinal Products for Human Use (2006) Guideline on the environmental risk assessment of medicinal products for human use. CPMP/SWP/4447/00. European Medicines Agency, London

Clark J, Summerton L, Smith E, Kampa E, Touraud E (2007) Discussion Document on Ecopharmacostewardship of Pharmaceutical Products. KNAPPE Deliverable available at: http://www.knappe-eu.org/fichiers/47-D5.1%20Ecopharmacostewardship%20discussion%20document.pdf

Council Directive of 12 June 1986 on the protection of the environment, and in particular of the soil, when sewage sludge is used in agriculture (86/278/EEC). Official J L 181, 4/7/1986

Council Directive of 21 May 1991 concerning urban waste water treatment (91/271/EEC). Official J L 135, 30/5/1991

Council Directive 96/29/EURATOM of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. Official J L 159, 29/6/1996

Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control. Official J L 257, 10/10/1996

Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom. Official J L 180, 9/7/1997, 22–27

Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Official Journal L 330, 5/12/1998

Council Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official J L 136, 30/4/2004

CVMP – Committee for Medicinal Products for Veterinary Use 2007 Guideline on environmental impact assessment for veterinary medicinal products – in support of the VICH guidelines GL6 and GL38. EMEA/CVMP/ERA/418282/2005. European Medicines Agency, London

Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for the Community action in the field of water policy. Official J L 327, 22/12/2000

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. Official J L 311, 28/11/2001, 1–66

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official J L 311, 28/11/2001 pp. 67–128

Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official J L 136, 30/4/2004, 34–57

Directive 2004/28/EC of the European Parliament and of the Council of (31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products. Official J L 136, 30/04/2004, 58–84

Directive 2006/7/EC of the European Parliament and of the Council of 15 February 2006 concerning the management of bathing water quality and repealing Directive 76/160/EEC. Official J L 64, 4/3/2006

Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration Official J L 372, 27/12/2006, pp. 19–31

Doerr-MacEwen NA, Haight ME (2006) Expert stakeholders' views on the management of human pharmaceuticals in the environment. Environ Manag 38, 853–866

Environment Agency (2003) Human Pharmaceuticals: Position Statement. http://www.environment-agency.gov.uk/aboutus/512398/289428/698017/?lang=_e

Holzmann T (2005) 2004 – ein wichtiges Jahr für die Umweltsicherheit von Arzneimitteln. Grußwort. In: Umweltbundesamt (ed.) 2005: Arzneimittel in der Umwelt – Zu Risiken und Nebenwirkungen fragen Sie das Umweltbundesamt. Texte 29-05. UBA. Dessau. 5–8

ICON – I C Consultants (2001) Pollutants in Urban Waste Water and Sewage Sludge. Final Report for DG Research. http://ec.europa.eu/environment/waste/sludge/pdf/sludge_pollutants_xsum.pdf

Jones OHA, Green PG, Voulvoulis N, Lester JN (2007) Questioning the excessive use of advanced treatment to remove organic micro-pollutants from waste water. Environ Sci Technol, 41 (14), 5085–5089

Kemp R (2002) Treatment of an EU directive: UWWTD, Compliance with the Urban Waste Water Treatment in Germany, Spain, England and Wales, and The Netherlands. Books on Demand, Norderstedt, Germany

Klein W, Denzer S, Herrchen M, Lepper P, Mueller M, Sehrt R, Storm A, Volmer J (1999) Revised proposal for a list of priority substances in the context of the water framework directive (COMMPS Procedure). Schmallenberg (Deutschland), Fraunhofer-Insitut: 97

Knacker T, Liebig M, Moltmann JF (2006) Environmental risk assessment. In: Ternes TA, Joss A (eds.) Human Pharmaceuticals, Hormones and Fragrances. The Challenge of Micropollutants in Urban Water Management. IWA Publishing, London, Seattle, pp. 121–147

Koschorreck J, Apel P (2006) A brief overview on the legal background and the regulatory instruments of the environmental risk assessment for pharmaceuticals in the EU, USA, Japan, Australia and Canada. In: Ternes TA, Joss A (eds.) Human PharmaceuticalsHormones and Fragrances. The Challenge of Micropollutants in Urban Water Management. IWA Publishing, London, Seattle, pp. 107–119

Kümmerer K (ed.) (2004) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. 2nd edition, Springer, Berlin, Heidelberg, New York

Kümmerer K (ed.) (2008a) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. 3rd edition, Springer, Berlin, Heidelberg, New York

Kümmerer K (2008b).Strategies for reducing the input of pharmaceuticals into the environment. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects, and Risk. 3rd edition, Springer, Berlin, Heidelberg, New York, p. 411

Kümmerer K, Schuster A (2008) Substance flows associated with medical care – Significance of different sources. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects, and Risk. 3rd edition, Springer, Berlin, Heidelberg, New York, p. 43

Montforts M (2005) Vorsorge vor Umweltrisiken in der Produktinformation von Veterinärpharmaka: Juristische Fallstricke und Methodologische Herausforderungen. In: Umweltbundesamt (ed.) Arzneimittel in der Umwelt – Zu Risiken und Nebenwirkungen fragen Sie das Umweltbundesamt. Texte 29-05, UBA, Dessau

Niquille A, Bugnon O (2008) Pharmaceuticals and environment: Role of community pharmacies. In: Kümmerer K (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects, and Risk. Springer, Berlin, Heidelberg, New York, p. 467

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official J L 136, 30/4/2004

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Official J L 396, 30/12/2006

Roorda J, Derksen A, Wortel N (2008) Challenging conventional sanitation options for health care units. Presentation at the International Conference on New Sanitation Concepts and Models of Governance [19-21.05.2008], Wageningen. Available online: http://www.sanitation-challenge.wur.nl/UK/Conference+Presentations/

Schlimm J (2005) Umweltbewertung von Arzneimittel in Deutschland – ein kurzer Abriss. In: Umweltbundesamt (ed.) Arzneimittel in der Umwelt – Zu Risiken und Nebenwirkungen fragen Sie das Umweltbundesamt. Texte 29-05, UBA, Dessau, pp. 5–8

SRU – Sachverständigenrat für Umweltfragen (ed.) (2007) Arzneimittel in der Umwelt. Stellungnahme. Nr 12, April 2007. SRU, Berlin

Stuer-Lauridsen F, Birkved M, Hansen LP, LützhØft HC, Halling-Sørensen B (2000) Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. Chemosphere, 40, 783–793

Umweltbundesamt (ed.) (2005) Arzneimittel in der Umwelt – Zu Risiken und Nebenwirkungen fragen Sie das Umweltbundesamt. Texte 29-05, UBA, Dessau

Van-Camp L, Bujarrabal B, Gentile A-R, Jones RJA, Montanarella L, Olazabal C, Selvaradjou S-K (2004) Reports of the Technical Working Groups Established under the Thematic Strategy for Soil Protection. EUR 21319 EN/6, 872 pp. Office for Official Publications of the European Communities, Luxembourg

VICH (2001) Guidance for Industry – Environmental Impact Assessments (EIAs) for Veterinary Medicinal Products (VMPs) – Phase I, VICH GL6, Final Guidance. US Department of Health and Human Services, Food and Drug Administration, Rockville

Wenzel H, Larsen HF, Clauson-Kaas J, Høibye L, Jacobsen BN (2008) Weighing environmental advantages and disadvantages of advanced wastewater treatment of micro-pollutants using environmental life cycle assessment. Water Sci Technol 57(1), 27–32

Chapter 18
Regulation and the Market-Incentives

Benoît Roig and Evelyne Touraud

18.1 Introduction

Pharmaceutical products (PPs) have been detected in surface, ground and drinking waters in Europe and worldwide. This has raised concerns about potential impacts on humans and organisms in the environment. Regulators are now acting on these concerns. For example, Sweden's Stockholm County Council has been working toward the assessment and classification of pharmaceuticals according to their environmental impact (see Wennmalm and Gunnarsson, Chap. 16, this book). An environmental label is being introduced in Sweden with the assistance of the pharmaceutical industry, which would enable the physician and the patient, where medications of similar action and efficiency are available, to select the treatment that is more environment friendly. The European Union is proposing more extensive environmental testing for product registrations while others are investigating mitigation measures such as take-back schemes, water treatment upgrades and labelling revisions (Wennmalm and Gunnarsson 2009). Other ideas involve incentives for development and market introduction of "green" pharmaceuticals and raising public awareness of the issues surrounding the environmental impacts of pharmaceutical products need strong support (Knappe 2008).

The impact of pharmaceutical products on the environment is not limited to end-of-life. To manage these impacts, eco-pharmaco stewardship approaches must be applied at all stages in the lifecycle of the pharmaceutical products. Indeed, companies engaged in chemical manufacturing are facing regulation demands to assess the environmental safety of new drugs and also increasing societal demands to reduce their environmental footprint In a first case, in contrast to veterinary substances, bad environmental behaviour does not lead to a denial of authorisation, but can have a very strong negative impact within the consumers.

B. Roig (✉)
Department of Biodiagnostic and Metrology, LGEI Centre, F-30319 Alès, France
e-mail: Benoit.Roig@mines-ales.fr

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_18,

18.2 Strategies for the Increased Development of Greener Pharmaceutical Products

The importance of considering environment and safety aspects in the early stages of process design is widely recognised and there are currently many efforts directed towards the discovery, development and use of more "clean technology" and "green chemistry". These could make a large contribution to the sustainability of the pharmaceutical industry when developing new PPs to ensure that they have as few adverse effects as possible whilst at the same time maximising their beneficial effects, leading to the development of a new generation of green and sustainable pharmaceutical products. For example, through KNAPPE project (www.knappe-eu.org) a number of eco-compatibility criteria have been identified to measure the overall environmental footprint of PPs:

1. *Derived from sustainable raw materials.* Most current drugs are derived from petroleum, which is a finite and non-renewable resource and is becoming an increasingly expensive raw material. In the long term, new drugs should therefore be derived from biomass or biotechnological conversion, which represent a renewable alternative to petroleum. Additionally, biotechnological processes usually work with aqueous systems and generate low product concentrations, at least compared with processes based upon fossil resources However, these approaches show limitations and drawbacks such as for example large-scale installations or energy requirement (Narodoslawsky et al. 2008). In the meantime, it is vital that the pharmaceutical industry gain a better understanding and control of the origin and sustainability of its raw materials and intermediates.
2. *Safe and clean synthesis.* New drugs should be designed using the principles of green chemistry and clean technology, minimising waste, reducing the amount of raw materials and maximising energy efficiency. These economical advantages are currently the drivers for introducing green chemistry/synthesis into pharmaceutical industries. But we need to distinguish, in pharmaceutical industries, green chemistry that involves safer and cleaner processes without considering the properties of the final products and green pharmacy that aims to generate more biodegradable and more environmental friendly substances.
3. *Maintained or enhanced efficacy.* It is of paramount importance that greener pharmaceuticals exhibit maintained or enhanced efficacy with limited side effects compared to any alternatives since they are extremely important to human health and, in many cases, can save lives.
4. *Reduced environmental impact at end of life.* It is also crucial that we consider the environmental impact of drugs at the end of life as an important factor while developing a new pharmaceutical product. Future greener drugs will need to be designed to have the desired effect within the human body and take into consideration their effect on ecosystems after having passed through the human metabolic system. This involves drugs that are more targeted (i.e. active at lower concentration) and generating less metabolites. The greener properties need to be also taken into account for metabolites in order to produce safer human by-products.

Consideration should also be given to excipients which are inherent components of PPs. Indeed, in final drugs, the active ingredient is always associated to one or several molecules in order to for example stabilise the active ingredient or to facilitate the uptake or to improve the transfer through the different membranes in the human body (vectors).

Finally, packaging also needs to be investigated because it represents a non-negligible part of the waste generated by the use of drugs. Each medicine is at least first wrapped in a blister or tube which is then included in a box. At the end of the life of the drug, these compounds are not consumed and have to be eliminated.

In parallel, more efficient take-back systems for unused/expired PPs need to be established in order to minimise the discharge of pharmaceuticals into the environment.

Ultimately, a quote considering on the one hand the active ingredient itself, its excipients and the packaging, and on the other hand the quality of the drug synthesis, could be proposed in order to rank the greenness of drugs. Different environmental classes of pharmaceuticals could be defined with a corresponding pictogram illustrating the high, good, weak or poor environmental quality. For a same pharmacological action, the patient and the prescriber could be able to choose the friendlier one.

Moreover, increase of the term of patent (an extra year for example) for greener pharmaceuticals should be a valuable incentive. Indeed, currently, the implementation of green pharmacy is an additional charge for pharmaceutical industries both in the design of the drugs as well as in the synthesis. Supplementary constraints are introduced without any advantages or benefits for the industry. Extension of the term of patent, from several weeks to several years would be very attractive mainly for economic reasons. In a same way, a medical policy promoting the priority use (prescription, delivery) of greener drugs would also be an interesting incentive. The example of generics in France is instructive. In the face of the low use of a generic compared to the patent molecule, the French government obliges patients who insist on the patent molecule to pay the difference between the two prices. In this way, the consumption of the generic increased rapidly (more than 30%).

In order to increase greener pharmaceutical products, some recommendations could be proposed such as:

- The implementation of tax or other incentives to make benign-by-design clean synthesis methods, green production technology and other stewardship approaches more attractive. This could be done alongside a campaign to increase awareness of the benefits of increased uptake of these methods (e.g. reduced costs in manufacturing through more efficient use of resources, avoidance of hazardous chemicals, reduced number of process steps, . . .) to the pharmaceutical industry, in particular amongst high-level managers to drive change within the business. In this frame, Pfizer, GSK, Astra Zeneca and others have introduced Green Chemistry into its medicinal chemistry through an educational program including the development of solvent selection and reagent selection

tools (Alfonsi et al. 2008). Moreover, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable works to inform and influence the Green Chemistry Research Agenda. This group of companies has agreed and published (Constable et al. 2007) a list of key green chemistry research areas from a pharmaceutical perspective and in the last 2 years has issued 4 research grants to support researchers working in these areas. Another aspect is the modification of the design of old pharmaceuticals leading more biodegradable products. Glufosfamide (http://www.thresholdpharm.com/sec/glufosfamide) is such an example but the approach is not very widespread.

- To move towards standardisation of methods to quantify the sustainability implications of PPs from different companies including consideration of all stages in the lifecycle of a PP and incorporating energy requirements. Metrics can provide a way to incorporate environmental data into cost and process factors in order to compare routes to different compounds and can also be used to predict and assess environmental issues. A number of green metrics have been reported (such as atom economy, environmental factor, effective mass yield, mass intensity, environmental quotient, reaction mass efficiency, carbon efficiency, . . .) that can be applied to measure the efficiency of a process/synthetic route. Typically process metrics do not include feedstocks or product fate, or energy usage, although it is important that they are applied with defined system boundaries, as with LCA (Life Cycle Assessment) (Graedel 1998, Curzons et al. 2007). Thus, benchmarking between products and synthesis would be facilitated as well as the differentiation between companies' environmental behaviour.
- The development of eco-compatibility criteria to score PPs on their environmental impact at all stages of their development including post consumer fate and use of these eco-compatibility criteria to develop a classification and labelling scheme to provide relevant and practical information for prescribers and users of PPs. This could be based upon an expansion of the Swedish classification and labelling scheme and could be implemented in other countries. However, such a classification has to be validated and should show the real interest and efficiency in other countries before being generalised. This action could represent a important incentive, especially if it becomes an additional criteria for the prescription, the sale or/and the use; in other words if it influences the market.
- To lobby for users to give preference of greener drugs (e.g. hospitals/national and local authorities). This involves making the medical actors (physicians, pharmacists, hospitals) more sensitive of the environmental concern. They have to be aware that the sustainable development concept can be applied in medicine and all healthcare activities. Indeed, most patients are very confident with their physician and/or pharmacist and consume medicines as prescribed or advised. That would need to create gathering at national scale between medical actors and environmentalist for a better consideration of environmental problem due to the healthcare activity. In concrete terms, a Danish hospital has become the second establishment in the world to adopt a landmark environmental policy on pharmaceuticals as those developed previously in Sweden. The purpose is to allow doctors to use environmental criteria when prescribing medication for patients, so that given a choice between two equally appropriate drugs they can choose the

one with the least impact on the environment. In France, for example, the C2DS (Community for a sustainable development in healthcare) is a community of idea and works, gathering more than 200 healthcare professionals and other actors of the hospital network (supplier, other employees. . .).[1] It involves several actions in direction of sustainable development such as the reduction of paper, water, electricity consumption, management of solid and liquid waste . . . It also gave an impulse in grouped purchase politics by taking into account environmental criteria (reduction of amounts, environment-friendly products. . .). In this context, and by considering an unchanged benefit for the patient, a purchase of greener drug could be stimulated.

These actions could modify and/or to influence the market of pharmaceutical products by the modification in the prescription, the advice in pharmacy or the use. So they should be considered as incentives for the manufacturers to go toward them.

On the other hand, a similar action to that for generic sale in France could be also envisaged for greener pharmaceuticals. In France, for example, the generic prescription was promoted by an increase in the doctor consultation rates with the condition of a higher generic prescription. Moreover, each patient is free to buy the branded products but have to pay the difference between the price of the generic and the patented product. Incentives to encourage sale of green pharmaceuticals could go through such politics of prices.

Eco-labels on product packaging for PPs represent a valuable communication method on the environmental impacts of PPs, although this would require a revision of guidelines and legal support. This could be applied to PPs with the same (or comparable) health efficiency but exhibiting different environmental behaviour in terms of degradability, persistence and toxicity, However, the pharmaceutical industry is suspicious about this because of the risk of unbalanced in the sale of medicine by using this argument. As for the security pictogram stamp on the packaging of cleaning products commercially available, one can imagine an eco-label stamp on the pillbox. But great effort is needed to obtain representative pictures of the criteria eco-label.

18.3 Strategies for Integrating Education and Awareness of the Issues Surrounding the Environmental Impacts of PPs

Education and awareness on Pharmaceuticals in the Environment have to be integrated in medical and pharmaceutical education and according the level of education.

In schools and undergraduate colleges, teachers are role models in inculcating good habits and moral values in students. Awareness programmes using simple language could be developed detailing the effects of inappropriate use such as misuse,

[1] www.c2ds.com

overuse or under use of medicines related to common diseases, the main message being to use medicine only when it is needed. Students in schools and undergraduate colleges could be informed about the harmful effects of using too many medicines: for example, when antibiotics are taken, the whole course of treatment should be completed as otherwise the microorganisms may become resistant to the antibiotics being used which may then be ineffective. Such simple messages should be identified and disseminated among persons taking their first college course (WHO 2006).

With postgraduate and technical schools, it should be possible to inform them on how to get information on medicines, their rational use, their environmental fate and impact. . .. Furthermore, modules on specific topics could be included in schools orientation programme.

A group approach or a large number of organisations should be involved in supporting or conducting public education work. These groups include professional organisations such as pharmacists and medical associations, international organisations such as WHO and UNICEF, governments represented by the Ministry of Health, non-governmental organisations and consumer groups, the universities and training institutions, the schools, the pharmaceutical industry and the media.

The professional groups such as medical and pharmacy associations should influence the members to gain commitment to the concept of public education and help in material development for projects. The international organisations could assist in sensitising governments and their partners to include education strategies in national drug policies and programmes, in producing training material and immobilising adequate funds. The government can assist in ensuring that public education is included in medicine-related policies and activities for systematic and sustainable implementation.

The NGOs should play a role in designing, implementing and supporting public education activities. The universities and other institutions should support the work through training of students, providing research and evaluation expertise and through linking good prescribing practice with rational use of medicines by the public. The schools are very important in creating an understanding of the benefits and risks of medicines and core information about their use. The materials developed need to be formally integrated into the school curriculum. The pharmaceutical industry is providing consumer information materials on medicines and financial support for dissemination of such information.

References

Alfonsi K, Colberg J, Dunn PJ, Fevig T, Jennings S, Johnson TA, Kleine HP, Knight C, Nagy MA, Perry DA, Stefaniak M (2008) Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. Green Chem 10, 31–36

Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer JL, Linderman RJ, Lorenz K, Manley J, Pearlman BA, Wells A, Zaks A, Zhang TY (2007) Key green chemistry research areas—A perspective from pharmaceutical manufacturers. Green Chem 9, 411–420

Curzons AD, Jiménez-González C, Duncan AL, Constable DJC, Cunningham VL (2007) Int J LCA 12(4), 272–280

Graedel TE (1998) Streamlined Life-Cycle Assessment. Prentice-Hall Inc, New Jersey

Knappe (2008) Information letter: What we need to know? From the patient to the environment, Knappe project (EU FP6 n°036864). www.knappe-eu.org/. . ./60-D6.4%20information%20letter.pdf

Narodoslawsky M, Niederl-Schmidinger A, Halasz L (2008) Utilising renewable resources economically: new challenges and chances for process development. J Cleaner Prod 16(2), 164–170

Wennmalm A, Gunnarsson B (2009) Pharmaceutical management through environmental product labelling in Sweden. Environ Int 35(5), 775–777

WHO (World Health Organisation) (2006) The Role of Education in the Rational Use of Medicines. SEARO Technical Publication Series, N°45

Chapter 19
Do Pharmaceuticals in the Environment Present an Investment Risk?

Andreas Holzer

19.1 Bank Sarasin's Sustainable Investments

The Sarasin Group is represented in 19 locations worldwide across Europe, the Middle East and Asia. By June 2009 it managed total client assets of CHF 80 billion and employed over 1,500 staff. Its majority shareholder is the Dutch Rabobank. Sustainable asset management is one of the three core investment styles offered by the bank. Here, stock selection is based not just on financial analysis, but also on environmental and social criteria. The sustainability of companies and industries is assessed by a team of nine experts on the basis of more than 70 criteria (Plinke 2007). In the bond segment, Sarasin's analysts not only award sustainability ratings to companies, but also to countries and supranational organisations. Over the past 10 years the volume of assets that Sarasin manages according to sustainable principles has soared from CHF 626 million to CHF 10 billion. This increase in volume and the integration of sustainability aspects into all Swiss private banking mandates as standard since the beginning of this year reflect the steadily growing importance of this investment style to the bank. At the end of 2007, the volume of sustainable investments (or socially responsible investments, as they are also known) in Europe was EUR 512 billion. This market grew by 86% over 2 years (2005−2007) and now accounts for around 3.4% of total assets under management in Europe.

19.2 Sustainability Aspects of the Pharmaceutical Industry

The pharmaceutical industry makes products that are of enormous benefit to society. Hardly any other industry makes such a direct contribution to saving human life. Precisely because of this, the industry has a high level of social responsibility and faces a number of relevant risk factors as far as sustainability is concerned: access to drugs for people on low income, marketing practices, ethics in clinical research, etc.

A. Holzer (✉)
Sustainability Analyst, Bank Sarasin & Co. Ltd, CH-4002 Basel, Switzerland
e-mail: andreas.holzer@sarasin.ch

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_19,

Table 19.1 Key sustainability issues for the pharmaceutical industry

Social	Environment
Access to medicines in developing countries	Energy consumed in production and transport
Access to medicines for low-income persons in industrialised countries	Emission of volatile organic compounds
Marketing practices	Waste
Efficacy/tolerability of products	Pharmaceuticals in the environment
Research practices (clinical studies, genetic engineering, etc.)	Environmental impact during pre-production
Lobbying	

The industry does not make the headlines as much when it comes to green issues, but even so the manufacture of drugs does have significant environmental impact (Table 19.1).

19.3 A "New" Theme: Pharmaceuticals in the Environment

One theme whose associated risks have not yet been properly clarified, but whose importance is steadily growing, is the level of drug residues in the environment. These active substances are released into the environment mainly after being excreted by patients on medication. Many substances can already be detected in surface water and in some cases in drinking water as well. What effect do these drug residues have on the environment and on anyone drinking tap water? The purpose of this chapter is not to analyse the natural science aspects in detail, but rather to describe whether (and exactly how) different stakeholders are affected and what consequences this theme has for pharmaceutical companies. This is relevant when investors come to assess the sustainability performance of drug companies.

The pharmaceutical industry faces the following risks with regard to the problem of pharmaceuticals in the environment:

- Introduction of regulatory constraints on production and use in connection with problematic substances. This would have a direct impact on the product offering and sales/profits.
- Potential damage to the reputation of pharmaceutical companies as an environmentally responsible industry.
- Water utility companies could try to pass on any additional water treatment costs to the pharmaceutical industry.
- In the case of significant negative impacts on the environment, a situation could even arise where green-minded consumers avoid the products in question – at least in the case of over the counter (OTC) medicines.

19.4 Concentrations Very Low, Risks Not Adequately Researched

The existing concentrations of drug residues in drinking water most likely do not present a health threat in the short term but are certainly not desirable. In most cases the concentrations in drinking water are in the region of a few nanogrammes per litre (see other chapters of this book), well below the therapeutically effective doses. Even so, very little research has been conducted into the long-term effects and the consequences of the gradual build-up and interactions of these different substances. One thing that has already been established without doubt, however, is that measured concentrations of certain active substances (hormones, Diclofenac) in the aquatic environment can have an impact on living organisms such as fish and algae.

19.5 Activities of the Pharmaceutical Industry

The approval procedures required by European and US drug authorities include ecotoxicological tests. The results mainly allow statements to be made on the drug's short-term impacts. Among the different pharmaceutical companies, the UK producer AstraZeneca is very actively doing research in this field. The company operates its own dedicated laboratory in the UK to research the effects on the environment of residual pharmaceutical substances. Other companies such as GlaxoSmithKline, Novartis and sanofi-aventis are also engaged in similar activities. Their research is intended to produce findings on how active substances behave in the environment (environmental toxicology, degradability, metabolism, dissemination pattern, groundwater prevalence, accumulation potential, etc.). This allows superior modelling and prediction, and subsequently more accurate assessment of the risks associated with the expected concentrations detected in the environment. On a sector level, the US industry association PhRMA has developed a model to calculate future concentrations of active substances in the environment (Cunningham 2008).

19.6 Green Drug Design

Experiences to date in the public debate show that drug manufacturers are for the most part held responsible for the potentially negative impacts of residual pharmaceutical substances. The key question is whether it is possible to design active substances which are just as medically effective but have far fewer repercussions on the environment (see Kümmerer, Chaps. 1 and 9, this book). Some pharmaceutical companies are trying to incorporate findings in this area into the initial development stage. AstraZeneca, for example, has started to prepare an information pack for each of its drugs in the development phase that provides information to all

the parties affected on the expected environmental impact during the usage phase. It would also make sense to incorporate the existing active substances into these research activities, as no equivalent data is available for many of the "old" drugs. Efficacy and safety obviously have top priority; a trade-off between the benefit to the patient and environmental protection is hardly acceptable. However, measures should be taken to ensure that drugs, especially those which do not have life-saving properties, should be designed to be as environmentally friendly as possible.

Such initiatives are still only limited in number in the pharmaceutical industry. The biggest pressure on companies is to fill their development pipelines. Nor are there any regulatory incentives to develop active substances with a positive environmental profile. The FDA already applies incentives to "steer" research activities in other specific areas. These include incentives such as extended patent protection, priority handling of applications, etc. for the development of orphan drugs (to treat diseases with comparatively small patient populations/also EMEA)(http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm) or more recently for neglected diseases (mainly prevalent in developing countries with no or inadequate therapy options)(http://www.bvgh.org/documents/BrownbackBrownanalysisFINAL.pdf). These mechanisms have proven themselves over time and the possibility of similarly promoting the green design of drugs should be explored further.

The most promising contribution to improving the situation comes (unintentionally) from biotech drugs. Proteins are supposed to be readily degradable (see Straub, Chap. 8, this book) and do not therefore accumulate in the environment. However, data that allow for a generalisation of these assumptions and findings are missing. Biopharmaceuticals have steadily grown in importance over the past decades. Despite being more limited in terms of potential uses, it is also worth keeping an eye on herbal and homeopathic remedies, which generally are supposed to have a neutral impact on the environment.

19.7 Water Utilities Concerned About Higher Costs

The theme also affects water supply companies facing higher water treatment costs. Research results to date show that drug residues are degraded and eliminated in different ways in sewage works. The efficiency of the sewage treatment process can be enhanced by expanding the purification stages, for example by including an activated carbon system. But this incurs substantial costs, may not be sustainable because of additional energy demand and total purification is not possible. Suitably positioned engineering and technology companies can exploit this. Proactive water utility companies have already conducted research into this theme or implemented initial technical measures. With increasing media coverage, pressure from consumers will grow. Water utilities are already stressing that the responsibility lies with the pharmaceutical industry.

19.8 No Plans for Tougher Legislation

On the legislative side, there have been no specific detailed regulations imposed to date on the environmental profile of drugs. The EU directives 2004/27/EC (medicinal products for human use) and 2004/28/EC (veterinary medicinal products) mention that "the environmental impact should be assessed" (see Kampa et al., Chap. 17, this book). Active substances are exempt from the registration process under REACH, the EU regulation on chemicals. It has been discussed whether certain active substances should be integrated into the EU Water Framework Directive. In view of the lack of knowledge about the distribution and effects of drug residues, however, it is unlikely that regulation will be extended to active pharmaceutical ingredients in the short to mid-term.

19.9 Consumers Wear Different Hats

Can – and should – clients of pharmaceutical companies (wholesalers, doctors, hospitals, patients) take into consideration the environmental sustainability of drugs? A first step in this direction has already been taken in an initiative by the Stockholm County Council, the state-owned pharmacy chain Apoteket and the Swedish Pharmaceutical Industry Association (see Wennmalm and Gunnarsson, Chap. 16, this book). Together they have drawn up and published a list of the most important environmental parameters for medicines. This means that especially doctors writing prescriptions will be able to select less problematic products. Comparable to consumer goods, it would also be feasible to label medicines that have a particularly good environmental profile – at least OTC products or veterinary drugs. One thing that is clear, however, is that most patients faced with a choice of two products would only opt for the one with a more environmentally friendly profile if its efficacy was equal to or better than the other product. In the case of veterinary medicines, it is also important that they are administered expertly.

19.10 Drug Residues Are Still a Controversial Topic

In other areas as well, interest has been growing in recent years both in business circles and among the general public as to how to tackle the problem of residual substances. In the case of the food industry, for example, this has resulted in lists of banned pesticides in food distribution and tougher approval procedures for pesticides. The public perception of the problem of drug residues will mainly be influenced by the results of drinking water analysis and new findings on the health effects and ecotoxicology results published in the media. One crucial development, for example, might be the confirmation of the link between drug residues and the problem of the rising incidence of male infertility. The socially desirable increase in

the use of medicines in poorer sections of the world population means the theme is also being transported to developing and emerging countries.

19.11 Sustainably Minded Investors Should Keep an Eye on This Theme

In the short- to mid-term it is likely that the pharmaceutical industry will not be affected by significant regulatory changes or product liability cases as a result of drug residues. However, initial findings on negative environmental impacts, the permeation of residues into drinking water and potential negative consequences for human health make it vital for pharmaceutical companies to look for ways to improve the situation. By acting proactively, the pharmaceutical industry can minimise its environmental, reputational, regulatory and liability risks. The corresponding corporate activities would be a positive development as far as sustainability is concerned.

References

Cunningham VL (2008) Environmental exposure modeling: Application of PhATE^{TM} and greatER to human pharmaceuticals in the environment. In: Kümmerer K (ed.) Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks. 3rd edition, Springer, Heidelberg Berlin, pp. 133−146

Plinke E (2007) Nachhaltigkeit von Unternehmen im Vergleich. Bank Sarasin, Basel

Part VI
Outlook

Chapter 20
Sustainable Health Products and Service Solutions in the Year 2050

Ludwig Metz and Klaus Kümmerer

20.1 Introduction

In this chapter we provide a vision of sustainable health products and service solutions in the future. Probably some will turn out to be wrong. However, forecasts can prevent certain unwanted developments. Another purpose is to trigger changes or initiate developments by playing the role of a self-fulfilling prophecy. In all cases, sustainability has proven to be a paramount paradigm not only of importance for the present but even more for the future.

The health care sector can be considered from different points of view. One is illness and therapy, another includes products and services offered by the industry and others. Criteria need to be established for sustainability in health care products and medical services. It has been successfully started in the manufacturing area where quite a lot has been achieved, especially focussing on synthesis, during the last decade. It is now time to concentrate on other fields such as prevention, diagnosis, treatment and post treatment, to name a few. For instance, if a treatment method is not well performed it might not be sustainable for the patient, the system and for the environment. Accordingly this applies also for post treatment and other aspects like the well being of the patient before and during diagnosis and therapy. Other issues such as "full reintegration of the patient into family and social life" or "payment for adequate treatment" need our attention, too.

20.2 Drivers

Current drivers for treatment by products are innovation in new diagnostic systems as well as diagnosis and description of new symptoms or syndromes. It has been partially recognized that after a syndrome was described such as chronic fatigue

L. Metz (✉)
D-93133 Burglengenfeld, Germany
e-mail: m-family@gmx.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_20,

syndrome or attention deficit disorder syndrome the number of cases diagnosed increased often very fast along with the usage of drugs and other means for therapy. Sometimes treatments are driven by the availability of (new) drugs or of new technologies for diagnosis. This however is not a total health approach.

Reasons for complex diseases are often unknown and precaution is only playing a minor role (examples are obesity, food safety, food quality, life style and so on). Negative effects for patients, such as unwanted and undesirable side effects, can result from insufficient and inappropriate diagnosis and treatments. This leads to high costs for the health system and finally for society.

Other examples are, if patient compliance is not met or if the package size is too big then a large amount of pharmaceuticals and packaging may end up in the waste stream or in the environment. This is neither beneficial for the system nor for the patients (see other chapters in this book). The current situation concerning sustainability must be improved; especially, if we understand sustainability as economic, social and environmental activities which will enable our generation and future generations to live on earth, still capable to support us.

20.3 Criteria for Sustainable Health Products and Services in the Year 2050

20.3.1 Manufacturing

In the future, information, molecular technology and sustainable manufacturing will certainly play a major role. This will lead to low cost, effective, mobile production units and production on demand. The production will be fast, easy, of high quality with no environmental impacts and will be sustainable. Ideally, the number of steps in manufacturing will be reduced to nearly one and the use of raw materials will be sharply reduced *during process syntheses*. The supply will be very effective and efficient, the quality high. Warehousing will become a story of the past since manufacturing units can be placed everywhere. Transportation will be dramatically reduced and remote control will be possible.

20.3.2 Prevention and Diagnosis

Prevention and diagnosis require available information in all areas. Total service and product responsibility will be in place. New technologies will provide remote control and body analysis and will inform the patient and contact specialists for early treatment. New systems will take over treatment and post treatment.

All these benefits will change medical treatment worldwide. The effect will be that companies, physicians, and pharmacists, will have different tasks.

Patients will be in a much more comfortable situation. Remote analysis, control and treatment will be standard. The use of pharmaceuticals will change and improper treatment will be minimised. Fewer hospitals and less physician visits,

remote treatment, lower production units, and optimized molecules will reduce energy, waste, pollution, and pharmaceuticals in the environment. Worldwide sustainable prevention and diagnosis can be imagined.

20.3.3 Services and Products

As for sustainable health services and products, the optimum criteria will be: treatment has no side effects and is target oriented. Treatment is easy and fast acting and shows excellent body tolerability. Correct dosage of medical products and intelligent devices e.g. for self-diagnosis, self-repair and feedback information (e.g. to the doctor via the internet or mobile units) will be made possible for everyone. An example would be a microcomputer integrated in the body which is continuously controlling the body and sending information if needed to the patient and doctor. In all these cases however data security is urgently required.

20.3.4 Post Treatment

There may be no need for post-treatment. However, if it is needed, a continuous body diagnosis e.g. by microcomputers and other micro-systems, nanotechnology and sensors is desirable.

20.3.5 Social Aspects

Diagnosis and therapy according to the above mentioned criteria should be affordable and available for everybody with the same high levelled quality worldwide. Questions related to this aspect are

- who will pay,
- who will benefit and
- what is fair.

20.4 Environment

All compounds should have no environmental impact. They should be easily, quickly and fully degradable (mineralized) after use and not persistent by all means. Furthermore, the parent compounds and the degradation products should not be toxic and not (bio) accumulate or accumulate elsewhere in the environment. They should be designed, that the environment (sun, water, wind etc.) will be used for complete mineralization. The best case would be for detoxification or full mineralization before leaving the human body after treatment.

20.5 Conclusion

Sustainable health products and service solutions are a serious topic for the future. Implementing them into real life will be important for industry and society. Sustainable development is needed in every industry but should be addressed especially throughout the health care sector.

Nobody knows what the situation will be in the future, e.g. in the year 2050 and what kind of diseases, diagnoses, treatments and other issues we will be facing. Therefore, we cannot speak about technologies which will be in place by then. But we can envision criteria and ideas for excellent sustainable health products and services.

Chapter 21
Summary and Outlook

Klaus Kümmerer, Maximilian Hempel, Hans-Christian Schaefer, and Florian Keil

21.1 The Presence of Pharmaceuticals in the Environment

The fact that pharmaceuticals are present in the environment where they impact on wildlife is widely accepted nowadays. Although there is general agreement that the presence of pharmaceuticals in drinking water does not constitute an acute risk to human health, there is uncertainty about possible long-term health and environmental risks caused by pharmaceuticals in the environment and a need for action has been identified. The public perception is often driven by concerns about the quality of drinking water and possible adverse or at least undesirable effects on humans and organisms in the environment. The presence of pharmaceuticals in the environment has therefore stimulated public discussion on drinking water safety and research into fate and effects of active pharmaceutical ingredients (APIs) and adjutants in water and soil, and the related risks is under way. However, learning about this problem can only be the starting point. For pharmacy in general a broader view is needed and it is about time to learn how pharmacy can be more sustainable in general.

21.2 Sustainable Pharmacy

A broader view is that pharmaceuticals are micro-pollutants and as such interfere with sustainable water issues. An even broader view is to bring into focus the whole life cycle of a pharmaceutical and the issues related to social, environmental and economic aspects of their use. All these various aspects and issues are summarized as "Sustainable Pharmacy" as a new paradigm. Despite the fact that the concept of sustainability in pharmacy is new it seems to be widely accepted as a valuable framework for further discussions, policy and research. This may be because of the

K. Kümmerer (✉)
Institute of Environmental Health Sciences, University Medical Center Freiburg,
D-79106 Freiburg, Germany
e-mail: klaus.kuemmerer@uniklinik-freiburg.de

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9_21,

acceptance of sustainability as a valuable objective in general, and the interconnectedness of sustainable pharmacy to sustainable or green chemistry. However, green and sustainable pharmacy is only in its infancy and what the word sustainable should comprise in this context is still very much open to discussion. One may for example argue that pharmacy always offers a benefit. However, the question is to whom? How should we deal with the fact that for various reasons not everyone has access to existing pharmaceuticals? Or how should we deal with the fact that manufacturing pharmaceuticals in less developed countries seems to be related to higher environmental stress and risks to the people living there? Theses few examples show that there is a long way to go to render pharmacy greener and more sustainable. As for the present status the following can be summarized:

Greening pharmacy is under way, but, greening is probably not enough. Instead, sustainability is the goal to be achieved. It should be discussed whether green and sustainable pharmacy could become part of a broader approach within the health care system and the general question of disease management, consumer protection, ethics and marketing.

21.3 Raw Materials

Due to the relatively low raw material input required for the production of pharmaceuticals discussions on renewable feedstocks and their limitations are not as prominent as they are in sustainable chemistry. Issues may be genetically modified organisms and the patenting of organisms. Here, ethics and economics play a prominent role.

21.4 Synthesis and Manufacturing

The biggest progress *in green* chemistry has been made in the field of syntheses and process engineering. Some new approaches and synthesis routes are already in place others are quite promising. Process design, which is closely related to the synthesis of pharmaceuticals, is including green aspects such as waste minimisation or avoidance of harmful solvents more and more. However, it has been learned that water may not always be the greenest solvent. Improvements in synthesis often go hand in hand with improvements in work place safety, energy demand and others that give financial advantages.

21.5 Drug Targeting and Drug Delivery on Site

On-site drug targeting and drug delivery can contribute to reducing the release of specific APIs into the environment. However, at the moment, it is not clear to what

degree and whether drug targeting and improvements in drug delivery on site can contribute to reducing the environmental burden by pharmaceuticals in general.

21.6 Benign by Design

The targeted design of pharmaceuticals is common practice in pharmaceutical industry, but inclusion of environmental aspects is not as yet a topic at top management level. Examples for its success must be provided. Here the role of politics, the public, regulators and market dynamics have to be explored more deeply. The role of so called biopharmaceuticals is still open. Are they generally better biodegradable in the environment – even after denaturation, e.g. in effluents of low or high pH? Blood stains on textiles teach the opposite. Are biopharmaceuticals in general where the future of pharmacy lies? Recent experience and research in anti cancer treatment has shown that a combined application of biopharmaceuticals ("bioceuticals") and "classical" small molecules may offer advantages. Does this hold in general?

There is a tendency in the development toward new APIs that possess increasingly lower activity thresholds. The total volume of pharmaceuticals reaching the environment could therefore be expected to decrease in the future. However, what is of interest, too, is the ratio of volume and toxicity threshold. Lower activity thresholds may lead to a higher risk for humans through unintended ingestion, e.g. by drinking water

21.7 Stakeholders

Measures that have to be taken by the stakeholders involved (doctors, pharmacists and patients, as well as other stakeholders) are promising, albeit difficult. The Swedish model (see Wennmalm and Gunnarsson, Chap. 16, this book) may serve as a promising example for such an approach. Proper information on use and proper handling of (unused or expired) drugs is urgently needed. Here, the environmental issue and the compliance issue can be linked to gain momentum.

21.8 (Advanced) Sewage Treatment

With regard to the global perspective, it should be mentioned that advanced sewage treatment as it is done in Europe, North America and other industrialised countries is not a global option for several reasons such as costs, water shortage, energy demands, or the timescales involved in establishing or changing to such technology. Presently, only 24% of the world population has access to sewage treatment. It also has its limitations in Europe, North America and other industrialised countries, too; the fact that to date there is no single treatment technology which efficiently removes all APIs from sewage, the problem that future APIs (or other micro-pollutants) may

be insensitive to the treatment technology chosen, or the question of whether relying on sewage treatment may further increase dependence on a centralized water infrastructure, which in itself may generate problems in some industrialised countries, are just a few reasons that should be mentioned here.

As for point sources there is evidence that contrary to expectations hospitals are not the main source of entry of pharmaceuticals into the aquatic environment. Therefore, separate treatment of such sources may only be an option for the reduction of the release of APIs into the environment in specific cases (e.g. where hospital effluents are strongly contaminated with particularly problematic APIs such as antibiotics or cytostatics). Another aspect is that in the case of improved sewage water treatment it is presumed that not the responsible producers of pharmaceuticals, but the public bears the cost of the sewage plant. Combinations of tools, technologies and different approaches on different local regional and temporal levels are possibly useful and have to be decided on a case by case basis.

21.9 Incentives

Incentives for greening pharmacy and pharmaceutical industries are cost reduction and other financial benefits such as prolongation of patent life time for better biodegradable pharmaceuticals. Corporate sustainable responsibility will also lead to savings in the company and to an improvement of the company's public image, which in turn will also result in economic advantages. It may also attract money from investors in the follow-up to environmental rankings provided by banks for ethical investment. Most measures in this field are probably related to costs and clear regulations. If environmental regulation on pharmaceuticals is tightened, the pressure to deal with environmental issues by companies will also increase and may trigger new developments. At the moment it is not clear to what extent the European Water Framework Directive is of importance or will include/should include pharmaceuticals. The same holds for other countries. However, on account of ongoing discussions it is to be expected that APIs and adjuvants will be included sooner or later. For patients, less environmental burden and clean and affordable drinking water may be an incentive for proper use and handling of more sustainable pharmaceuticals.

21.10 Outlook

The first International Conference on Sustainable Pharmacy (ICSP) has convincingly shown that the time has come to move from a problem to a solution perspective with regard to APIs in the environment. It was widely accepted by conference participants that the precautionary principle and a full life cycle perspective must be the guiding principles in this endeavour. The new paradigm of Sustainable Pharmacy was considered as a powerful approach that not only encompasses these principles,

but also conveys the inseparably coupled ecological, social, and economic facets of the problem. Concretely, Sustainable Pharmacy was discussed as to encompass a broad range of measures and techniques that might reduce environmental pollution by APIs. While for some, the need for immediate implementation was clearly emphasized, e.g. ensuring the proper disposal of unused or expired drugs, for others questions regarding their true potential remained open, e.g. drug targeting or drug delivery on site.

As the organizers of ICSP we conclude that the conference successfully contributed to introducing and substantiating the new paradigm of Sustainable Pharmacy. However, it also became clear, that important questions as to what the paradigm actually incorporates, how it can be operationalised, and how it relates to sustainable or green chemistry still remain open. Thus, most of the work still lies ahead.

Index

Note: The letters 'f' and 't' following the locators refer to figures and tables respectively.

K. Kümmerer, M. Hempel (eds.), *Green and Sustainable Pharmacy*,
DOI 10.1007/978-3-642-05199-9, © Springer-Verlag Berlin Heidelberg 2010