This book provides, in an accessible way, a summary of our current knowledge of the problems that surround pharmaceuticals and sustainable development. It is a small part in the larger puzzle of the measures that we must introduce in order to create good living conditions for future generations.

“We do not inherit the Earth from our ancestors, we borrow it from our children” is a quote that is often used to remind us of our responsibility.

This book is about that responsibility.

That is why it is important.
A Healthy Future

Pharmaceuticals in a Sustainable Society

First edition

Published in collaboration between Apoteket AB, MistraPharma and Stockholm County Council
Preface

The book you hold in your hands deals with a dilemma. How can we continue the vital use of pharmaceuticals without spreading toxic substances to the environment? We have known for several years that pharmaceutical residues in the water outside wastewater treatment plants affect fish in a way that causes males to become intersexual and feminised. Lack of more detailed knowledge is however still the greatest problem to developing a sustainable use of pharmaceuticals.

Environmental reports often present threats, alarms and unpleasant future scenarios. This is the case also for risks connected with the use of chemicals that have hazardous environmental properties. It is therefore gratifying to recall that since the first UN conference on the environment was held in Stockholm in 1972 we have witnessed the solution of several serious environmental problems. The depletion of the ozone layer has been halted, acidifying substance emissions have decreased and the multinational society is now making vigorous efforts to limit effects on the climate. All three of these examples show that with increased knowledge about cause and effect, apparently unbridgeable, complex environmental problems can be solved.

The MistraPharma programme will provide important, new knowledge about the problems with pharmaceuticals in the water environment. This research programme is unique in including all of the approximately 1,200 pharmaceuticals on the Swedish market. MistraPharma’s researchers make use of knowledge about the effects of pharmaceuticals on human beings and apply this to water-living organisms. The way the human body functions is in many ways similar to that of animals. Since pharmaceuticals are designed to have an effect on the patient, it is therefore most probable that pharmaceutical residues released into the environment also affect the organisms living there. In addition, the broad Mistra Pharma programme will also focus on substances with a high environmental risk and even include research to improve wastewater treatment technologies.
This book is the result of collaboration between Apoteket AB, Stockholm County Council and MistraPharma. In particular, I would like to thank the editorial committee, consisting of Bengt-Erik Bengtsson, Stockholm University, Bo Gunnarsson, Apoteket AB, Helene Hagerman and Karin Liljelund, Goodpoint AB and, finally, Åke Wennmalm, Stockholm County Council. All writers are responsible for their own texts.

I wish you an exciting reading and hope it will stimulate your curiosity in MistraPharma’s future work.

Ethel Forsberg

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Introduction
Margot Wallström,
Vice-President of the European Commission
Water is the most important prerequisite for life on Earth. It was in water that life had its origins, and without water life cannot continue. The water vapour that first condensed around four billion years ago became the water that we drink today. The cycling of water, from ocean to atmosphere, via rain to brooks and rivers and back to the ocean, creates the pre-conditions for us continuously having access to fresh water.

How can we protect this resource? Will our grandchildren and their grandchildren find natural springs that they dare to drink from, or will it be necessary in the future to consider all water from unknown sources as undrinkable?

Modern society has high demands for access to water of good quality. At the same time this society exposes our communal water resources to substantial stresses. It is primarily the release of chemicals into our lakes, rivers and oceans that creates the greatest challenges for the future. Pharmaceuticals are a part of this release and these challenges.

During my term as EU environmental commissioner REACH was developed, the programme that member countries are now in the process of implementing for the registration, evaluation and approval of chemicals. In connection with this effort, in 2003 I allowed a sample of my own blood to be analysed to find out which foreign chemicals it contained. The results were surprising, not least to me. Twenty eight different environmental toxins could be detected in my blood, and I naturally had no idea how I had been exposed to them.

It is now obvious to the majority of people that we cannot avoid being exposed to, and accumulating, a range of foreign chemicals in our bodies – chemicals that we come into contact with in our daily lives. Another, not insubstantial cause for concern is that these chemicals, for the most part, can cross the placental barrier to the developing foetus from the pregnant
mother, and that their breast milk eventually also will contain these chemicals.

REACH, the EU legislation governing chemicals, does not encompass pharmaceuticals. This is because pharmaceuticals are a particular group of chemicals, and as such they require special safety regulations. This does not mean that pharmaceuticals are exempt from environmental requirements. The current EU pharmaceutical legislation clearly states that pharmaceuticals can have negative effects on the environment and that these must be reported. The legislation also states that protective measures are required in specific cases. The new pharmaceutical strategy document that the Commission presented in the autumn of 2008 points out that measures to prevent a pharmaceutical from having negative environmental effects may need to be incorporated also into other EU regulations and EU directives. For many years the Commission has also provided support for a range of research projects that deal with different aspects of the relationship between pharmaceuticals and the environment. The question of what effects pharmaceuticals have on the environment is thus an active question within the EU.

Which path is the correct one to choose to guarantee both access to fresh water for future generations and to manage the extensive use of chemicals in our society? If we accept an increased outpouring of chemicals into our watercourses then many animal species will disappear and the ecological balance will be disturbed. Another obvious risk is that crops irrigated with surface water will be damaged. Therefore we must prevent the continuation of the release of chemicals into the environment.

I am convinced that REACH will be a great help in this effort. I also believe that the initiatives that are now being implemented with the help of “green chemistry” and “green design” to create pharmaceuticals that have a lesser impact on the environment are an important part of the solution. Naturally health care must develop systems to achieve the smallest possible release of pharmaceuticals and their decomposition products from patients. But I am convinced that we must also review the techniques used for wastewater treatment. Those chemicals, including pharmaceuticals, which arrive at wastewater treatment plants, to a certain extent end up in our lakes and watercourses. Some of these are retained in bottom sediment, from which they disappear very slowly. It is therefore important that all of the parties involved – manufacturers, health care, patients and wastewater treatment plants – help to guarantee that our water is of a high quality.
This book provides, in an accessible way, a summary of our current knowledge of the problems that surround pharmaceuticals and sustainable development. It is a small part in the larger puzzle of the measures that we must introduce in order to create good living conditions for future generations.

"We do not inherit the Earth from our ancestors, we borrow it from our children" is a quote that is often used to remind us of our responsibility.

This book is about that responsibility.

That is why it is important.
Pharmaceuticals and Sustainability: Concerns and Opportunities Regarding Human Health and the Environment

Christian G. Daughton, PhD and Ilene Sue Ruhoy, MD, PhD
The design, usage and practices surrounding pharmaceuticals play key roles in balancing the health and well-being of society with the requirement of reducing the impact of pharmaceutical ingredients on the environment. We must explore ways of designing drugs to be more environmentally safe, and we may need to reconsider how medication and medicine fits into the larger picture of health and wellbeing. This process can also bring positive economic outcomes to healthcare in general.

The design of pharmaceuticals and all of the practices surrounding their manufacture and usage are central for minimizing their impacts on the environment and increasing the sustainability 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).

The process of reducing environmental liabilities also has the potential to significantly advance and improve the medical and economic outcomes for healthcare, as natural collateral benefits. Key issues include: Can environmental sustainability be designed into the existing pharmacopeia, pharmacy, and healthcare systems so that considerations of potential environmental impacts feed back into improvements for healthcare and human wellbeing? What are the major factors that will shape the sustainability of healthcare for the future?

A confluence of advancements is currently at work in bringing sustainability in quality healthcare closer to reality. These include information technology, personalized medicine, medical genetics and epigenetics, green chemistry — 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.
Medicine has become synonymous with medication

Without question, pharmaceuticals play extraordinarily important roles in the protection and improvement of human and animal health and well-being. Treatment, palliative and curative, and prevention of disease, together with improved quality of life, are highly visible aspects of a global industry where sales in 2007 exceeded US$700bn.

The practice of medicine has become nearly synonymous with the administration of medications. The industry’s abilities and successes are a testament to over 150 years of innovation and R&D. The active ingredients in pharmaceuticals now total in the thousands and are arrayed over a large number of categories.

The immeasurable benefits of pharmaceuticals and of their ever-evolving sophistication, especially with the application of nanotechnology and biotechnology, are intertwined with and tempered by the ever-present risk of harm. Such risks include unexpected adverse reactions and outright toxicity, as from active pharmaceutical ingredients with narrow therapeutic windows, and from cytotoxics in particular. The risks also include abuse and addiction, and unintentional poisonings. Infants, children, the elderly, drug abusers and pets can be particularly exposed to such risks.

Formal systems have evolved worldwide to track adverse events. Major sources of this type of information gathering are the poison control centers (see for example WHO 2008) and through a variety of adverse event reporting systems. The latter make up what is generally known as the system of pharmacovigilance, whose formal origin was in France (Daughton and Ruhoy 2008).
Hidden roles of pharmaceuticals

Behind the scenes of the extremely visible, prominent roles played by pharmaceuticals in healthcare is another world where pharmaceuticals are surreptitiously involved in a wide spectrum of largely hidden roles. These can have 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, which serves to illustrate the interconnectedness of the activities and behaviors of humans with the environment. In the final analysis, human health and ecological integrity are intimately linked. Actions designed to maintain, alter or improve human health and wellbeing have consequences for the environment, which in turn can feed back to impact human health.

Drug residues from both human and veterinary usage can impact on the environment in many ways. They can contaminate:

- surface and ground waters via discharge or escape of treated and raw sewage, manure, or 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 contact, via residues transferred from skin (Daughton and Ruhoy submitted), and
- biota.

Some take up residence and become concentrated in sediments. These pathways can all lead back to human exposure via intake of drinking water and foods (Daughton 2007; Daughton 2008).

Interaction between healthcare and the environment

The visible and hidden worlds of pharmaceuticals have never been treated together as integral parts of the lifecycle of drugs. A major reason for this is that there has never been a forum to facilitate communication between environmental scientists and healthcare professionals. The invisible world of pharmaceuticals may need to become a central aspect of healthcare to ensure that the environment is protected (Daughton and Ruhoy 2008). In return, a collateral benefit could be the optimization of the delivery of healthcare in terms of both therapeutic outcomes and cost.

The various roles played by pharmaceuticals in healthcare are currently not in balance with the needs of the ecological environment, and arguably with the needs of public health and wellbeing. The WHO notes that proper man-
agement 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).

Vulnerabilities in the current healthcare system promote the avoidable introduction of active pharmaceutical ingredients into the environment as trace pollutants. The exposure of wildlife and other organisms to these residues creates risks for a broad spectrum of possible biological effects to occur, but the scope of potential impacts has yet to be extensively explored. These residues also undergo 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 them. Exposure is generally at very low levels, but has largely unknown consequences regarding health impacts (Daughton 2008).

**New interest in collateral outcomes**

It has only recently been proposed that actions to reduce the environmental impact of pharmaceuticals can also have reciprocal, collateral, positive outcomes for human health. This is despite the thousands of publications over the last two decades on various aspects of pharmaceuticals as environmental pollutants (US EPA 2008b). We can see positive effects, for example, as a result of modified medical practices like more prudent and appropriate prescribing, and as a result of reduced exposure to environmental residues (Daughton and Ruhoy 2008). Will 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? This might be a key test for green product design and development with respect to sustainable pharmacological care.

Beginning in the mid 1990’s Sweden has been an early pioneer in attempting to engage the medical community in extending their thinking and practice toward the consequences for the environment and to aim for the practice of ecologically sustainable healthcare. One of the earliest discussions targeted to the medical community regarding the need for ecologically sustainable medical care originated in Sweden (Eckerman and Martineus 1997). Even so, the more recent examinations of the need for standardized approaches for measuring healthcare waste do not focus on the actual usage of pharmaceuticals as a factor in sustainability (e.g., see: Tudor 2007).
Minimizing the environmental footprint

The environmental footprint of healthcare could be substantially reduced and the overall effectiveness improved if we implement any number of a wide array of measures across the many facets of the practice and administration of healthcare. The environmental residues would be reduced if new approaches to medical care were developed that eliminated leftover drugs. Therapeutic outcomes could also improve, for example because of improved patient compliance and reduction in over-prescribing and inappropriate prescribing. Healthcare expenses could go down by purchasing only those medications that would be fully consumed. Finally, 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.

The direction in which the practice of medicine has been headed holds tremendous promise not just for countless improvements in healthcare, but also with respect to greatly reducing its environmental footprint. Central to the new direction is its shift away from treating illness once it is manifest and instead toward a focus on prevention and wellness. Facilitating this is the emergence and convergence of personalized medicine, medical genetics and 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 other “omics”) and by advancements in computer technology.
Electronic systems and mining of healthcare data for improving the efficiency of pharmacy

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 organizations is IMS Health. Others include Verispan, Dendrite International and Wolters Kluwer. IMS Health mines monthly data from nearly 1 billion prescription sales, comprising 75 percent of all drug sales, from roughly 100 countries. At the same time, pharmacovigilance programs track adverse events linked to individual drugs. Noteworthy here is the redesign of the U.S. FDA’s Adverse Event Reporting System (AERS) under the “Sentinel Initiative”, which was initiated in May 2008. The objective of this is to create an integrated, electronic system for the nationwide monitoring of medical product safety (US FDA 2008).

Can digitalization reduce consumption?

Comparatively little is known regarding what percentage of each drug sold is actually ever consumed. This is despite extremely detailed data being available from drug sales and pharmacovigilance programs. The evolution of the practice of medicine has progressed faster in the delivery of healthcare than in achieving outcomes — life expectancy and quality of life.

Advancements in more tightly integrating these two into a more efficient healthcare continuum will serve as a major contributor in reducing the prescribing of medications that are ineffective for specific patients, or prescribing inappropriate doses or durations. Deficiencies in this regard contribute to unneeded excretion of active pharmaceutical ingredients and accumulation of leftovers eventually needing disposal — especially from drugs that are needlessly administered.

While these issues remain unaddressed, can existing data 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 questions that could be answered using 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?
- Do auto refills indicate a high probability of leftovers?
- Do prescriptions 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 unnecessary, 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 implementation of personalized medicine, especially the use of centralized electronic health records. Medicine has been increasingly adopting digital technologies, such as e-prescribing (including e-sampling), electronic health records and electronic decision support systems to, for example, ensure 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, while enabling consumers to assume more control over their own healthcare information.

The early stages of digital solutions targeted for the consumer range from those that are publicly accessible, like Microsoft’s HealthVault (www.healthvault.com) and Google Health (www.google.com/health), to those that are implemented by the healthcare industry, like the pioneering program of the Cleveland Clinic: MyChart (eclevelandclinic.com/cms/mychart.html); and the National Patient Health Information Network™ PHIN.

Most patient medical information is currently not digitized and therefore provides little value to physicians, pharmacists or to the patients themselves.

**Improved routines and disposal**

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. Harmonized and widely promulgated approaches are ultimately needed for drug disposal, unused drug collection take-backs, recycling that permits exchange of unused drugs among countries, evidence-based prescribing, pharmacovigilance, charitable contributions, and monitoring and tracking of the residues of active pharmaceutical ingredients in the environment and foods. One such proposal is a global pharmacogenomics network, specifically to study severe adverse drug 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 unused drug collection inventories holds the potential to provide invaluable insights regarding prescribing and dispensing habits, revealing areas that could be improved to reduce leftovers (Ruhoy and Daughton 2008). Leftover drugs are diagnostic of something amiss in the prescribing and dispensing system.

**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, 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). 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. Probably no other single development holds the potential for more profoundly affecting the use of drugs.
Personalized medicine 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 active pharmaceutical ingredients will occur. It will also probably lead to profound changes in the types and quantities of such ingredients introduced to the environment. Widespread implementation of advanced forms of personalized medicine could lead to the usage of a wider spectrum of drug classes, especially many new specialized classes. It could also lead to increased usage of certain individual active pharmaceutical ingredients. At the same time this may allow lower usage of most of these ingredients as a result of their use only for targeted situations where the probability of efficacy is very high. Reduced costs in drug development and clinical trials guided by personalized medicine 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, personalized medicine referred to the rather general notion of a patient-centered practice of medicine. The idea developed momentum in the late 1990s with the advancement of the Human Genome Project. It has since developed more concrete, specialized embodiments.

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 U.S. 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 or 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, a cost-justified payment system, for pharmaceutical treatment (Pollack 2007).

Better use, less waste

The ultimate hypothetical objective of personalized medicine is to aim for the optimal therapeutic response for a particular condition in a specific patient. 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 implement preventative measures.

This is achieved by selecting the optimal drug combined with the optimal dosage and dosing schedule for the optimal duration, while side-effects are
minimized. Concomitantly, personalized medicine is intended to be used to actively avoid the use of medications for individuals with a contraindicated predisposition. Personalized medicine could also facilitate earlier diagnosis and treatment, possibly permitting less sustained pharmacologic interventions.

Even the most widely used “blockbuster drugs” typically show efficacy in only 40–60 percent 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 per cent — only work in 30 or 50 per cent of the people”. For roughly the majority of usage, drugs are thus being used inefficiently at best, or inappropriately or imprudently at worst.

If the majority of drug usage is unwarranted, this leads to gross over-usage and accumulation of leftover drugs from non-compliant patients. These often comprise the poor-responders and non-responders. This excessive use then results in the unwarranted introduction of active pharmaceutical ingredients to the environment, from sources that could have been avoided, such as excretion and disposal. Poor metabolizers can also contribute a disproportionate fraction of parent pharmaceuticals to sewage via excretion. Personalized medicine could radically reduce or eliminate the unnecessary use of drugs in these instances by roughly half. Improved compliance and less wastage could result from increased trust or certainty by the patient in the efficacy of drugs.

**Nature versus nurture**

A prime objective of personalized medicine is to take into account the many differences between individuals and how these variables interact. Differences examined include genetics, such as slow and fast metabolizers and non-responders, gender, age, ethnicity, health status, idiosyncrasies in chronobiology, 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.

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. 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. In some instances it also allows for lower doses — or higher. 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.
Minimizing excretion of active pharmaceutical ingredients

For a truly sustainable pharmaceutical treatment model, considerations for environmental impact would need to be incorporated. This would require minimizing excretion of bioactive parent pharmaceutical compounds or metabolites. This includes conjugates in sewage that can be reconverted to parent forms. It would also require minimizing 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).

Numerous studies have verified the substantial 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 percent of cases were drug related and of these nearly 75 percent were deemed of moderate severity and nearly 10 percent as severe (Zed et al. 2008). The causes were classified as: adverse reactions (39.3 percent), non-adherence (27.9 percent) and use of the incorrect or suboptimal drug (11.5 percent).

Clearly, improvements in the areas of drug prescribing, for example via personalized medicine, 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 active pharmaceutical ingredients via excretion or disposal.

Safeguarding information

The advent of mainstream personalized medicine 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 IRB approvals.

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 and especially genetic exceptionalities in order to prevent discrimination. One example, in the U.S., is the Genetic Information Nondiscrimination Act (GINA) of 2008 (Hudson et al. 2008).

Continual advancements will also be needed in analytical chemistry for techniques that are sensitive 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 are also needed to make in-treatment monitoring more accessible to patients, thereby promoting proper dosage or biomarker titers and avoiding over-treatment.

Currently, genetic testing can reveal more than 1,500 medical conditions. Whilst current usefulness or efficacy is open to debate, personal genetic testing became readily available directly to the consumer in 2007. These tests primarily use DNA chips that allow analysis of thousands of SNPs; the first available being 23andme (www.23andme.com) and deCodeMe (www.decode-me.com), followed by a service offered by Navigenics (www.navigenics.com).

**Chemistry by design and improved drug delivery**

Clearly, personalized medicine has great potential for altering the usage of pharmaceuticals, both in terms of the quantities and types of active pharmaceutical ingredients. Thereby it can provide a potential for indirectly and passively reducing environmental impacts of active pharmaceutical ingredients 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 active pharmaceutical ingredient, beginning with the drug development process itself. Drug development is driven not just by measures of efficacy and safety, but also by factors such as drug and target discovery, drug design, synthesis, production and manufacture.

The long and complex decision process required for determining whether to proceed with commercializing a drug could be simplified using the factors that dictate environmental impact. These include persistence and potential for bioconcentration (e.g., Gunnarsson and Wennmalm 2008; Stockholm City Council 2008) as well as pharmacokinetics contributing to extensive excretion or conjugation or pharmacodynamics involving receptors in non-target
species. Active pharmaceutical ingredient candidates 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.
Green chemistry: Benign by design

In the U.S., 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 2008a). 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 pharmaceuticals and in striving to make drug-based medical care more sustainable. Opportunities for the application of green chemistry span the entire lifecycle of the pharmaceutical, ranging from drug discovery and design, manufacture, formulation, delivery and packaging, to the treatment of waste. Progress in any of the following, for example, can serve to reduce the footprint of active pharmaceutical ingredients:

- streamlining drug discovery, for example by capitalizing on ethnobiology, which in turn can catalyze the protection of endangered geographic locales (e.g., Mihelcic et al. 2007); computational approaches for developing candidate leads
- synthetic routes which have less reliance on hazardous reactants, reduced production of hazardous waste, or lower energy consumption, such as use of biocatalysis (Woodley 2008)
- optically pure active pharmaceutical ingredients that eliminate non-therapeutic isomers and reduce overall dose (Daughton 2003)
- chemical structures which are more amenable to microbial or physicochemical structural degradation, which lead to shorter environmental half-lives and reduced potential for bioconcentration in non-target organisms, and structural transformation to more innocuous end products
- structures or delivery formulations that facilitate the active ingredient in selectively reaching its biological target, thereby reducing dosage without the need to increase potency
- packaging that promotes a longer shelf life or provides accurate real-time indications of expiry status (e.g., Galagan and Su 2008), reducing the need for disposal, something that is especially important for those drugs sensitive to light, moisture or oxygen (e.g., Rosenberg et al. 2008)
- waste treatment approaches for destruction that can be adopted by existing waste and drinking water treatment facilities or even by health care and consumers.
Each of these aspects could be greatly expanded upon. A brief consideration of drug delivery alone reveals a bewildering spectrum of approaches that have been developed or are under development for improved targeted-delivery of active pharmaceutical ingredients. By making delivery to the target site more precise and efficient, doses can be vastly reduced while greatly reducing or eliminating side effects caused by systemic release. One example of this is provided by antibody-drug conjugate tumor therapy (Thayer 2008).

The armamentarium of effective pharmaceuticals could also be greatly expanded by making use of those existing molecules that have a high biological activity but which otherwise cannot reach their targets. Cellular uptake may for example be nil because of biophysical barriers. Nanotechnology will play an important role in advancing the effectiveness of new delivery approaches. The timing of dosing can sometimes be as important as physical targeting of the dose. An example of this is specially formulated chronotherapeutics, designed to release active pharmaceutical ingredients timed to the proper periodicities of rhythms (Smolensky and Peppas 2007).

On the down side, improved delivery could facilitate the increased use of much more potent pharmaceuticals. Even though the use of ultrapotent active pharmaceutical ingredients would reduce the absolute mass loadings of such ingredients released by excretion to sewage, the greatly increased potency of the active ingredient may serve to readjust the potential for effects in the environment.

Another potential problem is associated with alternative delivery routes such as dermal applications. The topical application of drugs can offer advantages in targeting, reduce systemic concentrations and avoid first-pass metabolism. But it also increases the amount of unaltered active substance that can be directly introduced to the environment, such as via release during bathing, or disposal of used delivery devices that still contain residual active pharmaceutical ingredients (Daughton and Ruhoy submitted). The equation for balancing environmental and human health aspects is a complex one.

**Smaller environmental footprint likely**

The expanding role of biotechnology in drug design could have major ramifications for environmental impact. Natural peptide and modified proteinaceous pharmaceutical ingredients continue to experience increased development as drugs. Insulin is still the most well 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 and poor bioavailability from the gut, as they are vulnerable to degradation by proteolytic enzymes or structural denaturation in the gut. Major advances in formulation and delivery technology are serving to protect these active molecules from degradation and denaturation in the gut and improve uptake. This could facilitate greatly expanded acceptance in healthcare (Levy 2008).

While not having received much attention by environmental scientists, this broad class of active pharmaceutical ingredients will probably have a considerably smaller environmental footprint than the more structurally stable synthetic active molecules. Those that do get excreted, even if they survive sewage treatment and environmental transformation or denaturing, would probably have considerably lower potential for resulting in exposure of non-target organisms due to their poor absorption across the skin or via the gut and propensity for degradation or denaturing.

Overviews and discussions of lifecycle considerations and green chemistry relevant to reducing the footprint of active pharmaceutical ingredients are covered by Clark et al. (2007), Constable et al. (2007), Gunnarsson and Wennmalm (2008), Henderson et al. (2008), Khetan and Collings (2007), Kümmerer (2007) and Tucker (2006), among others.
Pharmaceutical care can lead to improved healthcare and reduced environmental footprints

The practice of pharmacy has progressed through many phases over the centuries. This reflects 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 history, evolution and wide diversity of approaches in its implementation among countries have been covered in many publications over the last few decades (recent examples being Berenguer et al. (2004), Martin-Calero et al. (2004), Pearson (2007) and van Mil et al. (2004)).
The ways in which pharmacy is practiced will clearly have ramifications for environmental impact. The actual practice of pharmaceutical care is implemented using supplemental, collaborative or independent models of prescribing (Pearson 2007), where various degrees of autonomy for the pharmacist and degrees of involvement with the physician apply. Although pharmacy systems differ widely around the world, the authority to prescribe has been extended in various degrees to nurse practitioners, physician assistants and pharmacists. The ultimate implementation is the empowering of pharmacists to act as prime prescribers rather than just dispensers. In effect, this evolutionary step is transforming pharmacy from a customer-oriented practice to a practice focused on patient care. This step takes pharmacy beyond the sole focus of dispensing medications to the value-added dispensing of knowledge.

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 collaborations or partnerships between physician and pharmacist. Pharmacists could eventually become pharmacotherapy experts working as integral parts of medical practices (see: White and Latif 2006). Indeed, hospital care teams usually include a pharmacist for the purpose of enabling consultation on treatment implementation and monitoring of hospitalized patients.

**e-Prescription databases could minimize errors**

The traditional role of dispensing could transition away from pharmacists toward pharmacy technicians using increasingly more sophisticated automation and computerized knowledge systems. Dispensing could also be more tightly regulated with respect to quality control. One resultant outcome could be a substantial minimizing of dispensing errors. This would help to reduce the incidence of unused drugs.

By linking such systems with real-time databases for adverse drug reactions, as well as with information needed for personalized medicine, the risks of inappropriate prescribing 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 just one example.

A portion of such an electronic framework is just emerging with e-prescribing; as provided by the National Patient Health Information Network™ (PHIN) operated by Rx-Hub LLC and SureScripts (RxHub 2008). PHIN is
a real-time, nationwide, prescribing and information exchange network, which in part provides a patient’s medication history and decision support tools for physicians. PHIN will initially service over 200 million people in the U.S.

In-depth perspectives on electronic connectivity in healthcare are provided by the eHealth Initiative (2008) and the Markle Foundation (2008). In the U.S., 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).

The Future: PharmEcovigilance, medication’s footprint 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 can be formulated into a concept that incorporates pharmacovigilance as applied to both humans and the environment — pharmEcovigilance (Daughton and Ruhoy 2008).

Post-marketing surveillance for adverse effects in humans is performed under traditional pharmacovigilance programs. This existing monitoring system could be extended to also monitor for environmental impact. This could range from documenting sources of release of active pharmaceutical ingredients into the environment and occurrence in various environmental compartments, to impacts on non-target organisms.

There are currently no formal programs for monitoring the occurrence and trends of active pharmaceutical ingredients in the environment. Neither are there currently any formal programs for the detection of the emergence in the environment of new molecular entities (NMEs), something that is perhaps more important.

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, healthcare professionals and others such as the medical insurance and pharmaceutical manufacturing industries.
The future of pharmaceuticals will be shaped by intrinsic forces, including:

- 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 active pharmaceutical ingredients
- advancement in the many fields of “omics”
- 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
- 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).

Perhaps the central question we need to examine 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, balanced against the integrity of the environment?” Can the consumption of medication serve as an overall measure of societal and ecological health and wellbeing?

A perfectly working virtual healthcare system would generate no leftover medications. All humans and domestic animals would receive exactly the type, degree and duration of treatment required for optimal and cost-effective therapeutic and lifestyle outcomes. Excreted residues would have minimal impact on the environment.

Leftover drugs are diagnostic of any number of deficiencies in the chain of systems spanning from drug and package design, advertising, prescribing, and dispensing, to patient use. Reducing the footprint of medication holds the potential of benefiting both human health and the environment.

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Global Health Requires More Than Better Drugs

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The great discoveries in biology have equally great potential to improve global health. There are, however, many challenges. How do we handle the fact that one billion are overweight while one billion are undernourished? That drugs for poor people are a bad investment? Sick care or health care? New ways to find drugs also bring new technical challenges. The goal of global health is there, but the role of pharmaceuticals must be considered not only from scientific perspectives, but also from 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 20th Century realized major advances in health care and medicine 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. When coupled with advances in public health, this have led to significant increases in human longevity and decreases in infant mortality.
Global challenges require global cooperation

Despite these advances we face new challenges in the 21st Century from emerging diseases like HIV and avian influenza, resurging old diseases like TB, from resistance to our antibiotic armory, from diseases such as obesity, diabetes and cardiovascular problems, generated by our life styles, from neurodegenerative disorders like Alzheimer’s and Parkinson’s in a progressively aging population 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 the access to and availability of pharmaceuticals, albeit for differing reasons.

Thus, the promise of Ehrlich’s words remains significantly unfulfilled and the world faces challenges at this beginning of the 21st 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”. Their world-wide assault will demand unprecedented levels of global cooperation.

In addition this cooperation must take place in a world still significantly divided into rich and poor communities. Almost half the world live without adequate education, food, water and sanitation and without significant access to health care and pharmaceuticals. 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 markets continues. Indeed, some evidence suggests that 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.
**Tomorrow’s pharmaceuticals: The drug discovery process**

The traditional route of drug discovery has until recently been extremely successful, but is now undergoing rapid change. This process has been largely driven by observations of the biological activity of a natural product or synthetic substance on a physiological or pathological process; 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 (*Figure 1*).

**Old paradigm:**

Lead → Enzyme screen → Pharmacologic Model → Single candidate

**New paradigm:**

Genetically identified leads → Combinatorial chemistry → High throughput screen → 100’s candidates

*Figure 1.* A comparison of two paradigms of drug discovery.

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 (*Figures 1,2*).

*Figure 2.* Drug development in the 21st 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.
This in turn 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 (Figure 3).

Figure 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.

A number of drugs currently clinically available owe their efficacy to their being directed against a subset of diseases caused by specific genetic mutations. These drugs include Cetuximab, Imatinib, Trastuzumab and Gefitinib. It is likely that more efficacious pharmaceutical treatment of many other diseases will be accomplished through such pharmacogenetic profiling. Thus, hypertension remains a very poorly treated disease, despite the availability of well over 100 drugs in multiple pharmacological classes. This is because it is of multifactorial origin and the matching of drug and patient remains a largely empirical trial and error process, despite the fact that it has a common end-point of elevated blood pressure.

The technology of recombinant biology discovered in the latter part of the 20th century has made possible the facile expression of human proteins such as insulin, human growth hormone and erythropoietin, as well as the synthesis of new protein molecules, including humanized antibodies, for therapeutic use. These proteins can be expressed, in principle far more easily and cheaply, in plants and animals rather than in cultured cells. Thus human antithrombin is produced in goats and extracted from goats’ milk – a “farmaceutical”.

Phenotype

Emerging Pharmaceutical Sciences

Genotype
Unrealized potential

The presumed greater efficiency of the new drug discovery paradigm has, however, yet to be realized. There are several reasons underlying this. This can at least in part be attributed to the declining rate of new drug discovery by pharmaceutical companies. In 1996 there were 53 new molecular entities to only 17 in 2007.

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’s. Human biological complexity is therefore determined not by a simple “one gene = one protein = one target” model. It is rather determined by complex regulatory networks including multiple translations of the same gene, post-translational modification, epigenetic modification, multi-nodal cellular signaling networks and the newly emerging regulatory roles for small RNA sequences. 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 underly-
ing 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 are a therapeutic failure (Williams, 2004; Noble, 2008; Hellerstein, 2008).

Third, chemical space is huge. But biologically employed space, and hence exploitable space is very small, at least in our universe. For the typical small molecule drug there are thus some 10^62 possible molecular structures, while for the average size protein there are some 10^390 possible amino acid arrangements! 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. It is this very limited space that we must define and explore in the search for new pharmaceutical agents.

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. What remains are less tractable disorders, including the neurodegenerations of stroke, Alzheimer’s and Parkinson’s diseases and such disorders as autism.

Fifth, the dominant business model of the pharmaceutical industry has been the generation of “blockbuster” drugs with sales exceeding US$1 billion per year. With this model many smaller targets are ignored 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. For this reason the discovery and development of new antibiotics for example has been neglected and a major crisis in antibacterial therapy is unfolding with the development of resistance.

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. Drugs for tropical diseases that largely affect the poor world are not a priority item for development under this business model.

**Tomorrow’s drug development: Alternative models**

Whether a market-based system is the best approach to the delivery of health care and the development and delivery of pharmaceuticals is open to question. The USA practices a largely market-based approach with health
care outcomes, including infant mortality, adult longevity, access to health care, public health measures and satisfaction with availability, that are overall generally significantly inferior, despite greater costs, to those of the other member nations in OECD which enjoy a significant 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 proportion of its population in jail amongst the OECD members (Pew Charitable Trust, 2008). The USA model for health care delivery is thus not one that should be copied, although corporate influence worldwide may well attempt to ensure its dominance (Hegde, 2005; Starfield, 2000).

**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 – HIV, hypertension, respiratory diseases, cancer, and others – where intellectual property rights are additional barriers to availability. Second, the question of drug development for diseases that are dominant in the poor world for which there are few market incentives. These diseases include malaria, schistosomiasis, leishmaniasis and sleeping sickness. Of the approximately 1400 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”, as Medecins sans Frontieres express it. 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?

The current priorities for drug development can be measured from the public registry of interventional clinical trials, which is 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. 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.
Important to support new models

There are, 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 are two approaches for the delivery of existing drugs to the poor world. The latter permitted with scarce enthusiasm by the World Trade Organization through TRIPs. Both approaches present difficulties because of the real possibility of back import of the drugs to their country of origin, thus affecting the commercial pricing structure.

This approach is clearly not suitable for drugs for the tropical diseases that largely affect the poor world. So alternative structures are necessary. It is perhaps worthy of note that nations as colonial powers 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. This will increase 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.
These cooperative ventures will need very significant and ongoing levels of financial support. There is little reason to doubt 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. This is currently estimated to be approximately (a disputed) $1 billion (DiMasi et al., 2003). Given the cost of new drug development it is indeed likely that there will be more such cooperative arrangements in the future. These will include patent pooling or “open source” discovery (Srinivas, 2006 a, b). One such recently announced example is that between Merck, Pfizer and Lilly who will jointly develop new technologies through Enlight Biosciences.

**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, it is important to note that individual and societal overall health is determined by multiple factors. These include access to health care and how affordable it is, public health infrastructure and relative poverty level that contributes to “lifestyle”.

Although medicine is often credited with the overall increase in societal health in the 20th Century there is abundant evidence to suggest that it is only 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. Similarly, the incidence of respiratory TB in England and Wales had declined from 1840 by some 80 percent before antibiotics and vaccination were introduced.

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 vitally underpinning societal health (Sachs, 2005). In the absence of such measures the availability of pharmaceuticals alone will not suffice to create a healthy society, even if the pharmaceuticals are affordable.
Bad habits as a disease

Lifestyle and environmental factors impact disease in a variety of increasingly well known ways. They contribute to an expanding role for pharmaceutical intervention. Tobacco use is associated with cardiovascular disease and lung cancer, with world-wide death rates, of some 5 million per year. These are almost entirely preventable if the tobacco users cease their use of tobacco. Yet considerable resources are allocated to the discovery and use of pharmaceuticals to treat these tobacco-caused diseases.

The role of diet in disease is significant. This is particularly true with the increasing prevalence of adult and childhood obesity and the associated type II diabetes for which obesity is a major risk factor. Although there are clearly multiple origins of obesity, including genetic components, there is little doubt that lifestyle changes are major contributors. These are likely mediated through so-called susceptibility genes that increase the risk of becoming obese under the appropriate environmental conditions.

Human history has not been marked until very recently with a systematic abundance of cheap, high energy and palatable food – “fast food”. The availability of this fast food is facilitated by expansive and expensive marketing campaigns. Such availability has, together with newly sedentary modes of human behavior, resulted in the present overweight and obesity epidemic, first in the Western world, but now increasingly in the expanding middle classes of China and India.

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 antidiabetic and anti-obesity drugs. Considerable emphasis is placed commercially on the development of these multi-billion dollar markets while the urgent need for public health measures is relatively neglected by comparison.

The expanding scope of lifestyle drugs

Similarly, there has been an expansion of pharmaceutical marketing efforts into the broad area of so-called “lifestyle” pharmaceuticals. There has also been an expansion of the scope of existing diseases by broadening their definition. Disorders that are rare, but that have 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, 2005, 2006).

Wealth and health

Population health is ultimately determined by a number of factors including the overall wealth of the nation. Generally population health increases in accordance with national wealth, but in limiting fashion (for a discussion see Hertzman, 2001). Within individual populations, however, health is affected by individual socio-economic status. Increasing income inequality is 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. This is presumably linked to a more even distribution of public health and related infrastructure.
The road ahead: Promises and problems

Our previous century was one based on the great discoveries made in physics in the nineteenth and early twentieth centuries – clocks, steam engines, jet engines, typewriters, computers and the like. This century will be one based on the great discoveries in biology, beginning with the reading of the human and other genomes.

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 microarrays 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).

But this promised future will not arrive without a set of potential problems. These include 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.

Already most nations are facing serious challenges concerning cost and access to health care. With increasingly aging populations the cost and demand for access to new medicines will increase. There are, in principle, two limiting solutions. One is a free market model as essentially practiced in the United States, where health care is rationed by ability to pay. The other is 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 superior to those achieved in the United States (Commonwealth Fund, 2008; Nolte and McKee, 2008; Burd-Sharps et al., 2008).
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 of the gene(s) of origin and, subsequently, 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. When asked who owned the new polio vaccine, he responded by saying, “Well the people I would say. There is no patent. Could you patent the sun?”. This question remains a significant debating point. Pharmaceutical and biotechnology companies argue 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. Others argue that such upstream patenting not only increases the costs of gene-based drugs and diagnostic procedures, but that it actually impedes research and development by creating a scientific “anti-commons” (Heller, 2008; Heller and Eisenberg, 1998; Srinivas, 2006a,b; Triggle, 2005b).

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

**New safety concerns**

The conversion of protein drugs to generic form presents a particular challenge that does not exist with conventional small molecule drugs. Even minor modifications 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. This question remains unresolved.

Issues of drug safety and regulation will ultimately 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 restrictions in the 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).

A second issue of drug safety concerns environmental impact. Recent studies show that there are a vast array of pharmaceuticals in drinking water. These include antidepressants, steroid hormones, antibiotics, anticonvulsants and anti-inflammatories. 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. The problem can only become more serious with the introduction of new generations of biodrugs.
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Sustainable Development & Production of Human Pharmaceuticals
David Taylor, Strategic Director, wca environment
The research pharmaceutical industry is approaching environmental sustainability in two ways. Firstly by minimising its environmental footprint by increasing the efficiency with which it uses resources across all aspects of its business activities. Secondly, by reducing the environmental pressure exerted by that footprint by moving towards the use of less hazardous materials where that is possible. The objective is to minimise environmental impact whilst maintaining patient benefit.

A ‘sustainable’ business needs to satisfy three criteria: it must be economically viable, socially justified and environmentally acceptable. This article describes how the pharmaceutical industry works and how the research based companies are adopting a holistic approach to continuously reducing their environmental footprint whilst continuing to deliver benefit to the patient.

Sustainability is now the stated aim of most of the research companies. The environmental component of sustainability relates not only to manufacturing but also to product sales and distribution. Where possible, sustainability also applies to product design. Figure 1 (Clark and Summerton, 2008) shows the challenges and opportunities facing the industry. Rapid progress is now being made in most of these areas.
A costly business with high risks

The pharmaceutical industry is a very 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 supply sector.

The vast majority of new pharmaceuticals are thus developed by a small number of well known research pharmaceutical companies such as Astra-Zeneca and Pfizer. 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 around 10–20 percent by volume of the medicines being taken by patients. The remainder is produced by generic companies.

Product innovation is a very high risk business. It costs a very large amount of money, $500m to $800m, to take a new compound from the laboratory bench to the patient. Success rates are also extremely low. Only one or two out of every 100 compounds entering development results 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. The development process is lengthy however and it can take 10–12 years between the granting of the patent and the launching the product. This 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. As a consequence, 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.

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. Furthermore, since the drug is already a successful and well known product at the end of its patent life, sales and marketing needs are much less. Manufacturing costs are relatively small and thus the price of a new pharmaceutical falls dramatically after patent expiry.

This means that to survive, the research based companies need to constantly renew their product ranges. There is increasing evidence, however, that the rate of innovation is declining, (PriceWaterhouseCoopers 2007) whilst risk aversion in patients is increasing and pressure to reduce prices continues to grow. Consequently, the research companies are being driven to reduce development times, become even more innovative and use resources more efficiently.
Product Design – the key to success

In the research pharmaceutical sector, research and development is a major activity. In 2007, for example, AstraZeneca’s 13,000 researchers spent $10m every second on R&D in 17 principal centres across the world. This large scale activity has its own sustainability challenges related to the operation of the research facilities and to staff travel. In fact more energy is consumed by AstraZeneca’s research laboratories mainly in operating fume cupboards than by its factories. These issues are being addressed within the global programmes of reducing energy consumption. Most research pharmaceutical companies have set themselves targets to dramatically reduce their energy demand as well as cutting their emissions of greenhouse gases.

The objective of all this activity is to produce a regular stream of new medicines. A new drug will take from 8–12 years to develop from initial concept to marketable product and most candidates fail at one of the many hurdles along the way. At any moment a research pharmaceutical company will be undertaking research into anything from 50 to 150 potential drugs. A rigorous environmental risk assessment of all new medicines is now required as part of the EU Marketing Authorisation process (EC, 2006). Environmental evaluation is also needed to meet the requirements of other legislation, e.g. the eventual manufacturing plant will need to meet the consent conditions imposed by the local environmental regulator. This could apply to the product as well as to any waste materials involved in its manufacture.

Reducing drug residuals in the environment

Although the total mass of finished product produced by the industry is small, a large proportion of this enters the sewers by excretion from patients. Not all of this is subsequently removed during wastewater treatment. Consequently, very low residues of many pharmaceuticals can now be detected in the environment.

It is generally believed that these concentrations are far too low to pose any threat to human beings (Schwab et.al. 2005) and no immediate threat to wildlife (Cunningham et.al. 2006). There is still relatively little information on long term wildlife impacts, but the emerging conclusion from a major review of the ecotoxicological data for the EU KNAPPE Project (Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters) suggests that, with one or two exceptions, significant long term wildlife effects are also likely to be minimal (Boxall, 2008).
Nevertheless, like many industrial sectors the pharmaceutical industry is continually seeking to decrease the impact of its products on the environment. Current progress in research and development should lead to subsequent generations of drugs leaving lower residues in the environment. This does not mean that the industry is simply trying to make its products biodegradable. Biodegradable medicines can have other problems related to ‘shelf life’ and pharmacokinetics. They will still leave residues in the environment due to their constant input from multiple point sources, unless they degrade extremely rapidly.

In addition our knowledge of chemical degradation in the environment is currently far too rudimentary to be able to predict with any confidence how a new synthetic chemical could be modified to retain its pharmacological effectiveness and safety whilst increasing its rate of environmental decay. Research continues to be carried out in this area but it is unlikely that this will lead to any significant advances in drug design in the near future. There are many other ways, however, by which environmental residues can be reduced.

**Ideal medicine**

The objective of pharmaceutical research is to produce the ideal human medicine: one that is completely absorbed into the body, is effective in every patient, is specific to the disease, has no side effects and is subsequently completely metabolised in the patient to produce inert residues. It is clear that these are also many of the characteristics of a ‘green pharmaceutical’ and so improvements in drug design will inexorably lead to medicines with lower environmental footprints.

All of the major research pharmaceutical companies are, for example, very interested in the emerging area of ‘biopharmaceuticals’. These compounds, which are frequently based on proteins, now comprise up to 30 percent of new compounds under development. They have the advantage of being very specific in their mode of action. They need very low doses for effective treatment and, in most cases, they will be broken down to inert substances before excretion by the patient. It is thought that environmental residues of such medicines will be many orders of magnitude lower than that of current medicines.
Product manufacture: The necessity of quality control

The most important aspect of pharmaceutical manufacturing is quality control. When a medicine receives approval for marketing, the authorisation relates to both the medicine and to the method by which it was manufactured. Simple product sampling techniques, as used in other industries, are insufficient to ensure the quality that is needed and manufacturers are required to follow strict Good Manufacturing Practice guidelines, GMP (EC, 2003).

These involve a holistic approach to the whole manufacturing cycle. There is a requirement for extensive and rigorous qualification and validation of equipment and procedures, together with comprehensive documentation of every aspect of the process. Regulatory agencies undertake regular, often unannounced inspections and will expect to inspect any new manufacture prior to start-up.

These quality requirements are to ensure consistency between the medicine that was tested in the clinical trials and the product eventually used by the patient. In the past this often inhibited the implementation of improvements to the sustainability of manufacturing processes, as any significant changes triggered a requirement for further confirmatory clinical data. A more pragmatic approach is now being taken by the regulators, which enable improvements to the manufacturing process to continue to be made.

Manufacturing is complex...

The manufacture of pharmaceuticals represents a relatively small part of the activities and operating costs of a research pharmaceutical company. It is carried out in two stages. The first part, bulk drug production, produces the active ingredient, whilst secondary manufacture converts this active ingredient into a medicine that can be taken by the patient. The final product then needs to be packaged for subsequent sale and distribution.

Pharmaceuticals are produced in relatively small quantities, from a few kg per year for some anticancer drugs to a few hundred tonnes per year for more widely used medicines and a few thousand tonnes per year for some analgesics. This is in contrast to some bulk chemicals where 1000 tonnes per day production is common.

Unlike the majority of ‘bulk’ chemicals however, most pharmaceuticals are very complex organic molecules that have to be constructed using multiple synthetic steps, often involving the isolation of intermediate products. As
a consequence, process efficiency has historically been very low (Sheldon 1994).

**... but is getting greener**

Driven by cost and sustainability issues, the research pharmaceutical companies have in recent years become industry leaders in the introduction of green chemistry & technology techniques into their process design. Companies have developed sophisticated 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. Sustainability metrics are routinely used to compare alternative process routes (Curzons *et al.* 1999). This has led to major improvements in efficiency in these complex syntheses 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.
Smart formulation and packaging

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 quickly react 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 the cleaning of equipment to avoid cross contamination. These wastes are however readily treatable using modern technologies, such as reverse osmosis and activated carbon.

Minimising packaging has also been the focus of much effort in the industry, although this has sometimes been impeded by other, often desirable, legislative requirements; e.g. loose tablets now have to be encapsulated in blister packs and pharmaceutical labels must now include information in Braille (EC, 2004). Both these laudable pieces of regulation have unfortunately resulted in increased amounts of packaging.

As discussed above, 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 concentration effluents

Outsourcing – environmental friendly effectiveness

In recent years there has been an increasing tendency for more and more of the manufacturing operations in research pharmaceutical companies to be contracted to third parties. One aim of outsourcing is to increase sustainability by improving operational efficiency and save costs.
The larger research pharmaceutical companies were originally largely self-sufficient, carrying out their own R&D, Manufacture, Sales and Distribution. But outsourcing has always played a part in the industry. In some cases a company might not have had the technical capabilities to undertake part of the synthesis of the active ingredient and would have had this step undertaken by a contractor. In other cases third party contractors would have been used to provide alternative sources of supply to provide security in the event of an interruption in production at the main manufacturing site. As cost pressures have increased on the industry over the last ten years, ‘outsourcing’ has been recognised as a method to decrease costs whilst potentially improving operational efficiency.

Most drugs have a relatively short useable patent life, usually of less than 10 years. In order to get a new drug onto the market as soon as possible, the manufacturing plant needs to be established before the product has received approval from the regulators. If the product is extremely successful, this manufacturing plant may not then be big enough to cope with demand. But if the product fails to gain approval from the regulator the plant will not be needed at all, nor will it be useful after patent expiry. It is thus a more sustainable practice to contract the manufacturing of the product to a number of external suppliers, who can be expanded to cope with any unexpected demand.

In the last ten years, the contract fine chemical manufacturing sector has become very experienced, highly competent, cost efficient and successful. Since contract manufacturers are focussed on chemical manufacture, they can be more efficient in their use of energy and resources than their pharmaceutical customers. Contractors in the newly industrialised countries (NICs) such as Brazil, China and India currently have a major competitive advantage as a result of very low (although increasing) wage costs. Concerns often remain, however, about quality, security of intellectual property and health, safety & environmental issues. Recent investigations showing very high concentrations of active pharmaceutical ingredients in the effluent from a wastewater treatment plant serving drug manufacturers in Patancheru in India (Larsson et al. 2007) and similar findings in China (Li et al. 2008) have highlighted the potential problems. This reinforces the need for pharmaceutical companies to take great care both in their selection and particularly in their continued performance monitoring of contractors. At present most pharmaceutical outsourcing remains with contractors in the developed world.
Introducing a green sales force

At first sight Sales & Distribution may appear to have little relevance to sustainability. But there are 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 that 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 amounted to 730 million kilometres, 90 percent of which was associated with sales and marketing. This distance is equivalent to 18,300 times around the world and produced 150,000 tonnes of greenhouse gas emissions (AstraZeneca, 2008b).
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 is introducing both ‘hybrid vehicles’ and ‘flex fuel’ vehicles into its sales fleet. In Brazil, where ethanol fuels are widely available, more than 96 percent of the cars in the Marketing & 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 percent by 2010.

**Right amount at the right place and time**

To fulfil demand, the product has to be distributed from the factory to the pharmacy. This inevitably leads to the emission of greenhouse gases, even if distribution is not a major emitter. As an example, only 10 percent of AstraZeneca’s total greenhouse gas emissions come from freight transport. But improvements are nevertheless being made. Bulk transport with final packing of products at the marketing companies has reduced demand for freight whilst efforts have simultaneously been made to use more environmentally friendly packaging options.

For example, volumes can be reduced significantly by using slip-sheet techniques in air freight rather than conventional pallet. Furthermore, reusable blankets have replaced polystyrene boxes for temperature-controlled transport wherever possible. 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. 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. Demand for
a particular medicine, however, is variable and difficult to predict since the requests come 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, distributor and pharmacy to meet all requirements. Most pharmaceuticals, however, have a limited shelf life and this policy has resulted in very significant amounts of out-of-date 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. This will reduce overall wastage whilst ensuring continuity of supply to the patient.

Making information available

Until recently, information on the environmental impact of individual pharmaceuticals was not available to either health professionals or patients. In 2005 however, Stockholm County Council introduced and made publicly available, an environmental hazard classification scheme that covered approximately 30 percent of the medicines used in Stockholm (Wennmalm & Gunnarsson, 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, in conjunction with expert representatives from international pharmaceutical companies (Mattson et.al. 2007). The information is made available on the website of the Swedish Doctors Prescribing Guide (www.FASS.se). There is currently interest in extending coverage across the European Union.

In theory, this information can be used by the doctor and patient to ensure that the patient receives the most effective medication that produces the least environmental risk. In practice, after taking both efficacy and cost into account, further choices are however 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 – less than two percent – of existing pharmaceuticals fall into the highest risk category. Consequently, classification schemes of this type provide a welcome improvement in transparency, but their environmental benefit is likely to be modest.
Disposing of unused medicines

Most pharmaceutical residues in the environment result from excretion of the medicine by the patient and this is difficult to avoid. Another potential source of pharmaceutical residues is unused and out-of-date medicines. In the past, patients were encouraged to dispose of these medicines into the household toilet, since this would ensure that they would not be available to children. This is, of course, no longer an acceptable practice since it leads to pharmaceuticals being directly released to the environment. Unused medicines should, where possible, always be returned to a pharmacy which can ensure that such material is destroyed.

Doctors also 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 by using short term prescriptions (7-14d). When the efficacy has been established, the patient can be provided with longer term supplies (28d).

The desire to minimise unused medicines needs to be balanced by the much more important requirement to encourage the patient to adhere 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.
References


Global Health Requires a Sustainable Supply of Pharmaceuticals
Barbro Westerholm, Professor Emerita, Member of Swedish Parliament
Health is a human right. Consequently, it is also a human right to have effective and safe pharmaceutical treatment, regardless of where one lives in the world. The World Health Organization, WHO, have taken large steps towards developing pharmaceutical supply in the world, for example by compiling lists of essential medicines, in other words those pharmaceuticals that are the most important for a country to have available. But there is still a lot to do, amongst other things in expanding research, developing distribution channels and trade terms and conditions, educating personnel and combating counterfeiters.

The average life expectancy is increasing worldwide. This applies both in the more developed countries and in the less developed. The average life expectancy has increased by almost 20 years during the second half of the 1900s (Figure 1). This is partly due to decreased child mortality, and partly due to the elderly living increasingly longer.

Underlying these successes is the improved health of the general population. This is due to access to better housing, better hygiene, food, fresh water, clothing, education and medical treatment methods. In this pharmaceuticals have, and continue to have, an important role.
Everyone has the right to be healthy

But the differences in average life expectancy and health between different parts of the world are still large, due to economic resources, living standards and access to health care and medicine. This would not be the case if the situation was in line with the United Nations (UN) Charter, article 25, point 1, from 1948. Here it states that:

“Every individual has the right to a standard of living that is adequate for his own and his family’s health and wellbeing, including therein food, clothing, housing, healthcare and necessary social privileges, in addition to the right to security in the case of unemployment, sickness, invalidity, the death of a spouse, old age or other reduction in capacity to provide for himself, under circumstances over which he has no control.”

These aspects of the Charter are now incorporated into international, regional and national conventions and legislation. These should protect both individuals and groups of people, so that nothing and nobody can impinge on their fundamental liberties.

Within health care and medicine it is the World Health Organization (WHO) that is the driving force in the efforts to convert the right-to-health goal of the UN into a reality. In 1977 the member states of the WHO supported the goal of ”Health for all by the year 2000”. The organization then initiated a
comprehensive effort to formulate sub-goals and prepare the groundwork for achieving these. The organization identified primary care as the fundamental basis of health care and medicine, and pointed out that an effort to rationalise the use of pharmaceuticals would be an important part of the work towards achieving that goal.

A first step in the WHO efforts towards the right-to-health was to adopt the so called Alma-Ata Declaration concerning primary care (see www.who.int). The participating member states adopted the declaration at a meeting in Alma-Ata in 1978. The declaration states, amongst other things, that: “...health is a fundamental human right and the achievement of the best health possible is a very important worldwide social goal”.

Already at that time, the WHO recognised access to essential medicines, their quality and their use as one of the cornerstones of primary care, and therefore also in the efforts to achieve the goal of “Health for all”. Since then more than 100 countries have introduced the right-to-health into their national constitutions and laws. In September 2005 the WHO member states decided to also write the promotion of human rights into their legislation, and the right-to-health is also included in this.
Rational use of pharmaceuticals

The WHO has, not least since the Alma-Ata meeting, worked to promote rational use of pharmaceuticals. The incorrect use of pharmaceuticals is a serious, global problem. The WHO estimates that more than half of all pharmaceuticals are prescribed, dispensed or sold in an incorrect way. In addition to this, half of the patients use them incorrectly. They over consume, under consume or take them incorrectly, which results in the squandering of resources and leads to greater risks of complications.

The WHO advocates 12 key measures to stimulate better use of pharmaceuticals:

1. Establishment of a multidisciplinary national body to coordinate policies on medicine use
2. Use of clinical guidelines
3. Development and use of national essential medicines list
4. Establishment of drug and therapeutics committees in districts and hospitals
5. Inclusion of problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Use of independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Use of appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff

Everyone should be able to have the pharmaceutical they need

The right-to-health requires that everyone can access effective treatment methods, including pharmaceuticals. But what pharmaceuticals these are varies the world over, depending on the age distribution of the population and their disease panorama.

In the developed parts of the world, where the average life expectancy is high, it is diseases such as diabetes, cardiovascular disease, dementia, depression and tumour-based diseases that are predominant. It follows that the predominant pharmaceutical requirements are those for the treatment of these diseases. In the developing countries it is infectious diseases that
account for half of the disease burden. Currently 4.8 billion people live in these countries, which amounts to 80 percent of the world’s population. For this portion the needs that are paramount are for antibiotics, chemotherapeutics and agents to treat malaria. But with an increasing life expectancy also in the developing countries their needs will become more similar to those of the industrialised nations.
Most important of all – access to essential medicines

Since the WHO adopted the “Health for all” strategy the organization has strived towards fairness in access to pharmaceuticals worldwide. In 1977 the WHO presented the first list of essential medicines. This was then an item on the agenda the following year at the meeting in Alma-Ata.

Essential medicines are those pharmaceuticals that meet the prioritised health requirements of a population. They are selected based on the diseases that are present in that population and they should have a proven efficacy, safety and cost effectiveness. The view of the WHO is that these should always be available in adequate amounts. Other terms that are used to describe essential medicines are “essential drugs”, vital pharmaceuticals and necessary pharmaceuticals.

The draft of the WHO Medicines Strategy 2008 – 2013 was made available for consultation on the Internet on 24 July 2008. This presents the experiences gathered during the work with essential medicines since 1977. It shows that the essential medicines concept has become increasingly accepted globally. At the beginning of the millennium more than 150 countries had a national list of essential medicines. It is beyond question that this work has been a success and that the WHO has been unsurpassed in this field. Efforts to promote essential medicines are consequently one of the most important successes of the WHO in the area of health.
The work has also contributed to the development of guiding principles for pharmaceutical regulation in over a hundred countries, as well as principles for approval and the allocation of generic names. Thousands of professional specialists from the developing countries as well as from the industrialised nations have been educated in, among other things, pharmaceutical assessment, manufacture, pricing, supply and the marketing of pharmaceuticals. Systems have been developed to enable comparisons of pricing and availability and so on. The WHO has also published an International Pharmacopeia that is used worldwide and sets the quality standards that apply to new essential medicines. The organization has also created a global network for the follow up of adverse effects of new essential medicines. The network focuses especially on malaria, HIV and children.

The model list of essential medicines is updated every two years and in 2007 the first list for children was released. In addition to 150 countries having national lists, more than 130 countries have drawn up national treatment recommendations. Many countries also have ongoing initiatives to stimulate a rational prescribing of pharmaceuticals.

The importance of traditional medicine was also recognised at the 1978 Alma-Ata meeting. Since then the use of these treatment methods has increased dramatically worldwide. There are even countries that have included natural remedies on their list of essential medicines. In 2007 there were 48 countries with a national policy on alternative medicine and over 110 countries had sets of regulations pertaining to these methods.

**Strengths and weaknesses**

The strength behind the WHO pharmaceutical programme lies in the term “essential medicine”. Today this is associated with fairness, cost effectiveness, good leadership and recognition of the needs of the poor and underprivileged. The weakness lies in lack of funding. This means that much of the knowledge that is available does not reach the developing countries and, to some extent, neither do the pharmaceuticals they need.

But there is still a long way to go before we reach the goal of everyone having access to the pharmaceuticals they need. Today every third person on Earth lacks access to essential medicines. Underlying factors are poverty and lack of purchasing power in many countries. When a pharmaceutical is not available in the public sector, many patients must buy their medicines from the significantly more expensive private sector, or do without medical treatment altogether.
Other important underlying causes are deficiencies in the quality and funding of health care. The costs of pharmaceuticals also play an important role, as many people in the developing countries do not have any health care insurance. They must therefore pay their own pharmaceutical costs.

**The national and global goals of the WHO**

In order to improve access to essential medicines at reasonable prices the WHO pharmaceutical programme proposes a number of goals at national and global levels:

At the national level
- abolish tax and import duty for essential medicines
- update national pharmaceutical policies
- update the national model list of essential medicines
- adopt a generic substitution policy for essential medicines
- search for ways to minimise distribution-based trade price increases in essential medicines
- guarantee access to essential medicines within public health care and medicine
- regularly monitor pharmaceutical costs and availability.

At the global level
- encourage the pharmaceutical industry to use differential pricing in order to reduce the costs of essential medicines in the developing countries where it is not possible to substitute the pharmaceutical with a generic drug
- further promote the production of generic pharmaceuticals
- increase the funding for research into and development of pharmaceuticals that are relevant for developing countries, for example dose and administration forms for children and the most neglected diseases.
Commercial health

Patent regulations can contribute to high pharmaceutical prices and consequently hinder access to medicines, not least in the developing countries. During the twenty years that patent protection is valid no external actor can make use of the invention without the permission of the holder of the patent. If there is no equivalent substitute for the product on the market, a monopoly situation is created. The holder of the patent can exploit this, not least to recoup the money that has been invested in the research that has formed the basis for the approval of the pharmaceutical. Pharmaceuticals are expensive to develop, but comparatively cheap to manufacture. The owner is therefore dependant on the protection the patent gives in order for the money that has been invested in the research to be recovered.

For companies it is rational to adjust their prices to what the market can pay. This can mean that prices are higher in high-income countries and lower in developing countries. But this model does not work in the area of pharmaceuticals for two reasons. Firstly it can result in pharmaceuticals that are sold cheaply to developing countries being re-imported to the high-income countries. Secondly, many of the high-income countries have price regulations for subsidised pharmaceuticals. The company then runs the risk of the high-income countries using the price in the developing countries as a benchmark, as a result of which the company will then lose the income that is intended to cover their research costs.

In 2003 the World Trade Organization (WTO) adopted new regulations to improve the availability of pharmaceuticals in developing countries. With the support of a so called compulsory purchase license the developing countries are given the opportunity to import patented pharmaceuticals. This means that the WTO agreement on trade related intellectual property, TRIPS (Trade-Related Aspects of Intellectual Property Rights), has been amended.

An ordinary license is a permit that the holder of the patent can choose to grant to another party to allow them to make use of an invention. A compulsory license is a special situation where a party is granted permission to make use of a patented invention without the permission of the patent holder. Originally a compulsory license could only be issued for an internal market.
The new regulations allow WTO members to issue compulsory licenses for pharmaceuticals. But they only apply to pharmaceuticals that will be exported to developing countries with serious health problems who cannot manufacture the pharmaceutical themselves.

In the autumn of 2007 the EU approved the amendment to the TRIPS agreement on compulsory licenses (2007/768/EG). The EU view was that the developing countries without their own pharmaceutical production would thereby have easier access to vital pharmaceuticals. The Swedish National Board of Trade, however, takes a less positive view in their analysis of the new regulations.

The Board stresses that the question of access to pharmaceuticals is very complex. Trade regulations form only a small part of this. The Board mean that it is therefore difficult to isolate and judge the value of the new regulations in TRIPS by themselves, especially as there are not so many examples to base judgement on. By analysing the new regulations and the current situation regarding access to pharmaceuticals the Swedish National Board of Trade has drawn the following overall conclusions about the new compulsory license regulations:

• The new regulations have been introduced in order to enable access to patented pharmaceuticals. They have so far not been utilised fully, which to a large extent can be explained by the fact that countries such as India have had the capacity to manufacture low cost copies of pharmaceuticals. There is much to suggest that the scope for use of the new regulations will now expand when these countries also introduce patent protection within the pharmaceutical area.
When it comes to low-income countries the chances that the new regulations will enable pharmaceutical imports are small. The market potential is far too limited. All of the preconditions will seldom be able to be fulfilled. The new regulations are therefore not likely to improve general access to pharmaceuticals in developing countries. They can however work for particular countries or products.

The provisions in regional free trade agreements can hinder use of the new regulations or make their use impossible. The same is true if undefined terms and conditions in the new regulations are interpreted in a restrictive manner.

The use of the new regulations can be facilitated by regional collaborations in order to increase the size of the market. Technical and financial aid can be worthwhile, for example to support the importing countries in fulfilling the administrative requirements that the regulations demand.

Source: The WTO decision on compulsory licensing: does it enable import of medicines for developing countries with grave public health problems?, 2008

Distribution and access to competent personnel

Access to pharmaceuticals also requires functional distribution channels, competent pharmacists, doctors and other health care and medical personnel.

In the western world pharmaceutical distribution is well developed. In principle anyone who needs to be treated with a medicine can collect it from a pharmacy or drugstore. In countries with a poorly developed infrastructure and weak economy the situation is not so good.

It is vital that there are highly educated pharmacists. In this area the FIP (International Pharmaceutical Federation) have developed principles for how developing countries can achieve a good pharmaceutical service. In 1992 the FIP issued standards for good service for pharmacies and drugstores and presented these at their congress in Tokyo. In 1993 the organization formulated a declaration that contained health promoting measures, access to pharmaceuticals and medical device products, self care and improved prescription of pharmaceuticals and improved pharmaceutical use based on efforts by members of the pharmaceutical profession (Good Pharmacy Practice – GPP).
The Federation is realistic and recognises that there is a lack of pharmacists. The primary health care personnel in the developing countries must instead therefore have pharmaceutical knowledge. These personnel must be given a fundamental pharmaceutical education and receive further training about how pharmaceuticals should be used.

**Development of new pharmaceuticals**

In 2004 the World Health Organization (WHO) published the book *Priority Medicines for Europe and the World*. Key conclusions. The authors of the book were Warren Kaplan and Richard Laing, supported by a group of the world’s most eminent experts within the field. The authors’ conclusions were the following:

- There are many diseases that contribute to the disease burden both in Europe and globally. Successful research, both in the area of the development of new pharmaceuticals and in the area of improved medicines, would benefit both Europe and the world.
- Antibiotic resistance and widespread epidemics of influenza are two of the most serious threats to global health. These require coordinated efforts, for example by EU countries. The increased production of influenza vaccines in European countries is an urgently needed first step prior to an unavoidable influenza epidemic.
- Smoking is an underlying causative factor in the most common diseases that affect both Europe and the world in general. Measures to discourage people from starting to smoke should be the most prioritized intervention. At the same time the EU should support research into pharmacological methods to help people to stop smoking.
- The development of new pharmaceuticals in Europe can be improved by reforming the regulations and the systems of prioritisation. The authors recommend a research programme that focuses on these areas and that includes the biggest stakeholders in the areas that these efforts concern.
- The possibility of a good treatment outcome can be improved by improving the distribution of the pharmaceuticals, something that also requires research in order to be carried out in practice.
- The development of new pharmaceuticals should also encompass patient groups such as the elderly, women and children. These have particular needs in terms of products, dose and methods of administration.
- New incentives must be created where the market has failed to provide new pharmaceuticals, for example to combat tropical diseases and other neglected diseases, so that the results of basic research are not lost. Such incentives should result in clinically important products being developed.
There are frameworks for stimulating clinical research into HIV/AIDS, tuberculosis and malaria due to the EDCTP (European and Developing Countries Clinical Trials Partnership), but gaps exist when it comes to research into other diseases. The report recommends expanding the mandate of the EDCTP to encompass other neglected diseases and that society, as well as industry, should support these developments.

Information technology developments have provided new opportunities for comparing and evaluating the worth of new pharmaceuticals following their approval. Use of such methods should invigorate the situation in Europe and reduce the time taken for a pharmaceutical to reach the market.

**World Health Organization recommendations**

The report *Priority Medicines for Europe and the World*. Key conclusions recommends more research to develop new pharmaceuticals within the following areas:

- antibacterial resistance
- pandemic influenza
- cardiovascular disease
- diabetes
- cancer
- acute stroke
- HIV/AIDS
- tuberculosis
- rare diseases
- malaria
- Alzheimer’s disease
- osteoarthritis
- chronic obstructive pulmonary disorder
- alcohol related diseases
- liver disease, dependency illnesses
- depression in the elderly and the young
- post-partum bleeding

Even if research is ongoing in a number of these areas there are still gaps in our knowledge of these diseases and their treatment.
There are continuous efforts by the WHO to try to satisfy the world’s pharmaceutical needs. In May 2008 the World Health Assembly adopted a strategy and plan concerning public health and the development of new treatment methods (WHA61.21) designed to help alleviate the shortcomings identified in the report issued by the WHO in 2004. The strategy and plan encompasses not only the development of new pharmaceuticals, but also the development of new medical devices. These should be developed based on current ethical principles, they should be available in sufficient quantities, should be effective and safe, accessible and reasonably priced and should be used in a rational way. The strategy also provides guidelines for improving exchange of knowledge, financing and monitoring of the effects of pharmaceuticals and their adverse effects.
Strong stance to combat counterfeiting

During recent years the WHO have increased their interest in counterfeit pharmaceuticals, which are a serious threat to health. A counterfeit pharmaceutical is a product that has been falsely labelled with regard to its identity and/or origin, intentionally and with intent to deceive. Counterfeit pharmaceuticals can contain everything from toxic substances, in different admixtures and doses, to inactive substances.

The WHO estimates that between 8 and 10 percent of the medicine that is sold throughout the world is counterfeit. In some countries this figure can be as high as 25 percent. The situation is worst in countries where pharmaceutical inspection procedures are lacking. The WHO opinion is that the problem is increasing and that by 2010 the proportion of counterfeit pharmaceuticals will have doubled.

In the developed countries the appearance of counterfeit pharmaceuticals in traditional distribution chains is becoming increasingly common. In the developing countries it is primarily Internet trading that poses the biggest risk. But there are no exact figures for sales of this type and so it is not possible to be accurate about how much can be classed as counterfeit copies or copies that do not contain active substance. According to a report from LIF (Swedish Association of the Pharmaceutical Industry) these may account for at least half of the pharmaceuticals sold via the Internet.

The counterfeiters have become more and more ingenious in avoiding discovery. They set up dummy companies, find weaknesses in customs checks, use false documentation to obtain ingredients for essential medicines and use similar methods to obtain manufacturing equipment in order to copy the original product. According to a report from the Council of Europe the majority of the packages are manufactured in India, the United Arab Emirates and China.

In the proposal for the WHO action plan 2008–2013, “Medicines Strategy 2008 – 2013”, there is a status report and presentation of future intervention measures to combat counterfeit pharmaceuticals. The working group IMPACT, The International Medical Products Anti-Counterfeiting Taskforce, have been working since 2006 to coordinate efforts within and between countries to stop the manufacture, trade and sales of counterfeit pharmaceuticals in the world.
IMPACT has defined those areas that they will concentrate on, namely legislation, the adaptation of the legislation and other sets of regulations, technology development and communication. The public must be informed about the risks of buying pharmaceuticals via the Internet and from non-approved sources. The working plan also includes the distribution of existing documentation and developing a web-based Rapid Alert System to make this accessible in all regions. IMPACT also advise that a thorough attempt is made to combat the sales of counterfeit pharmaceuticals via the Internet and that there should be an initiative focusing on the specific needs and problems of the countries south of the Sahara.

The Council of Europe has in their report on counterfeit pharmaceuticals ascertained that coordinated intervention efforts are required, such as the EU directive that binds member states to carrying out actions to improve traceability and documentation during the distribution of pharmaceuticals. In addition the Council proposes that a unit is established that, at the European level, will be responsible for the coordination of cross-border efforts, initiate networks, registration systems and databases. The Council will also make the penalties for counterfeiting more severe and establish common legislation to make trade in counterfeit pharmaceuticals more difficult. The Council also proposes a common system of sealing in order to further minimise the risk of counterfeit pharmaceuticals being able to enter the distribution chain undetected. The EU Commission has developed a proposal for a directive that has been distributed to the member states for comment at the time of writing.

**We know what we have to do**

Health is a human right and consequently it is a right that the citizens of the world should have access to effective, safe and cost-effective pharmaceuticals. But to be able to provide these rights we must invest in basic research as well as clinical research into the underlying causes of different diseases, not least when it comes to rare diseases. In addition, industry must develop pharmaceuticals for those diseases we do not have a cure for today and improve those medicines we already have. In all probability the companies and the social institutions must establish effective collaborations in order for these efforts to succeed.

We need a functional national pharmaceutical inspection system and a functional system for price setting for pharmaceuticals. But the pharmaceuticals themselves are not enough. Access is also required to an infrastructure
that can distribute them. A publically funded primary health care and the presence of personnel within health care and medicine who have sufficient knowledge of pharmaceuticals and how they should be used are also essential. Even the general public needs to know what factors are important to think about when using pharmaceuticals. In addition, both health care professionals and the general public need to understand the risks of counterfeit pharmaceuticals and how we can avoid them.

So the knowledge of what we have to do exists. But it requires political desire, strength and stamina to reach the goal – to provide the world with a sustainable supply of pharmaceuticals.
Sustainable Pharmaceutical Distribution and Trade
Stefan Carlsson, CEO
Apoteket AB
To achieve sustainable distribution and supply of pharmaceuticals there are a number of factors that everyone included in the pharmaceutical chain must bear in mind, develop and nurture. By so doing, we will be able to secure the supply of pharmaceuticals for everyone far into the future.

If all parties in the chain, from manufacturer to customer, cooperate, we will be able to get as close as possible to the best medical benefit and the least environmental impact. This constitutes a reasonable interpretation of the meaning of sustainability within the area of pharmaceutical supply. No one will be denied medical treatment for environmental reasons.

If you play with the thought of how our life, lifespan and security would be if no pharmaceuticals were available, you quickly realise how important it is for our society to have a secure access to pharmaceuticals and that we use these in the best possible way. This is a concern for society that reaches far into the future. In order for society to continue to benefit from good pharmaceuticals our management of pharmaceuticals must be sustainable.

With a sustainable pharmaceutical distribution and trade we in our generation will be able to continue living a good life while maintaining our existing wealth and standards. We must however do this in such a way that the coming generations are also given the same opportunities. We can live off the rent but not off the capital. We must for example:

- Develop pharmaceuticals with consideration taken to illnesses that may be important to prevent, relieve and cure in the future. Pharmaceuticals effective for tumour and viral diseases could be such areas.
- Use antibiotics in such a way that they also in the future provide effective means for the combating of infections.
- Provide scientific institutions and the pharmaceutical industry with the means for further developing our pharmaceutical arsenal. Giving support to education and research that could be beneficial within the pharmaceutical area is one example.
- Keep side effects, miss-use and environmental impact of pharmaceuticals under control.
The best medical benefit with the least environmental impact

How can we get the best medical benefit from our pharmaceuticals while keeping the environmental impact as small as possible? There have previously been many initiatives and many are also now ongoing to increase medical benefit and achieve as great relief and cure as possible. This is the Holy Grail for the pharmaceutical industry, the guiding principle for the regulatory authorities, the ambition of the practitioner, the goal for the pharmacies and the greatest wish of the customer and patient.

From a perspective of sustainability, the second part – minimal environmental impact– is however also very important. All parties have a responsibility to work towards an environmental impact that is as low as possible.

The retail trade can do much to both increase the benefits and lessen the environmental impact. They can provide customers and prescribing doctors with information and advice, as well as review all of the medications a customer uses and in what dose. To prescribe medication for shorter instead of longer periods of time may also have a positive effect on the environment. The amount of pharmaceuticals that then have to be discarded if the customer must stop the ongoing treatment will be less than if a larger package had been given out.

Transportation also effects the environment

The environmental impact from pharmaceuticals is not only caused by biologically active substances entering land and water. Transportation in the distribution chain, which may generate greenhouse gases, constitutes another impact risk.

We must therefore consider environmental issues when decisions regarding establishing and logistics within the pharmacy market are to be made. In the Swedish pharmacy market 200 suppliers provide 150 million pharmaceutical packages for 90 million pharmacy visits. This means transportation of both goods and people. There are a number of factors of great significance here for our possibilities of minimising the total environmental impact. How easily accessible are the pharmacies? Is it possible to coordinate pharmaceutical transportation and customers’ purchasing patterns?
There is a huge potential for improvement in Sweden to better coordinate transportation of pharmaceuticals to the pharmacies. It would also be desirable if authorities were to promote environmentally friendly products and systems when making decisions regarding payments to suppliers and retailers.

**From one end to the other the chain is long before the pharmaceutical reaches the person in need**

The process is long from a medical idea to a pharmaceutical being available on the market with the potential of preventing, relieving and curing illness and disease. No link in this chain must be allowed to fail. Developmental work prior to the introduction of new approved pharmaceuticals must function, the manufacture cannot fail, either in volume or quality, distribution must reach all the way to the one in need of the pharmaceuticals on time and use of the pharmaceutical must be optimal.

Pharmaceutical distribution is well developed in the West. All who are in need of a pharmaceutical are able to get it. There are not really any logistical hindrances and so far the economical hindrances are manageable. The situation may be quite different in other parts of the world. Logistics as well as economics may be poor and it is not even certain that pharmaceuticals have been developed for treating local illnesses and diseases. Examples of this in developing countries can be pharmaceuticals for HIV and against malaria.

**Pharmaceuticals must be available**

Pharmaceuticals must be available when the need arises for an individual or within the healthcare services. This means that a nationwide distribution network must be in place that continuously provides society with pharmaceuticals – today this is in practice the pharmacies. It is however not always economically justifiable to establish pharmacies that will only supply a very small number of inhabitants. In such cases it is necessary to create complementary functions to ensure supply.

In Sweden a broad network of pharmacies are complemented by almost as many authorised agents who can sell pharmaceuticals. An authorised agent can deal with prescriptions and prescribed medications as well as sell a limited selection of non-prescription drugs. Healthcare, care centres and hospitals additionally have access to emergency doses that can be given to a person who cannot otherwise immediately get hold of the medication through the ordinary supply network. By telephone or via the internet it is
also often possible to order those pharmaceuticals a customer will take over a long time period and thus knows the long-term need of in advance. These can then be delivered by post to the customer.

As important as the geographical availability is the temporal availability. A pharmacy closed on Sundays is not much help in a case of emergency. Also in this case we must balance the requirements against the practical and economical conditions, and use the most suitable alternative ways of distributing pharmaceuticals.

**Pharmaceutical subsidies are important**

Many pharmaceuticals are so expensive that it would be impossible or would impose a heavy economic load on many people if they were to pay the total cost themselves. This is especially true for patients that have to use medications over a long time. In most of the countries in Western Europe society therefore pays a significant part of the pharmaceutical cost; pharmaceutical subsidies exist. Since many pharmaceuticals would be unavailable for many people without the subsidies, this is an important aspect of availability.

One way of increasing availability in countries without the economical resources necessary for pharmaceutical subsidies would be to apply a pricing structure for pharmaceuticals which is far lower than that of the world market. Countries with stronger economies will have to accept such lower prices in those countries.
**Good service means many things**

Pharmaceutical availability is not only however determined by generous opening hours and the physical location of pharmaceutical sales outlets. The assortment available at the pharmacies must be balanced in order for the customer to be provided with as good a service as possible. This means that as many of the customers as possible should be able to get the medicine they need directly. There are in addition pharmaceuticals which may be used only rarely but, if so, are of uttermost importance and are of critical significance for stopping the disease progression. A pharmacy needs to have such pharmaceuticals in store even if they are more of an economical burden than good business for an individual pharmacy.

A person who suffers from poor health and is in need of medication does not in most cases have the ability to decide which pharmaceutical therapy would be the most suitable for them. It is simply not reasonable to expect the patient or customer to have the knowledge necessary to choose his/her own medication. He or she needs help.

The medication of choice for each individual should always be decided by the medical need. If other factors also are allowed to direct the choice, the medical benefit from the pharmaceutical treatment could be reduced. Factors that might contribute to people not getting the best pharmaceutical treatment could be marketing by pharmaceutical manufacturers and pharmacies, pharmacy policy regarding the supplies they store and inconsistent obligations to provide the best pharmaceutical.

There are some prerequisites for a reliable pharmaceutical supply. The customer must feel secure in the knowledge that these prerequisites are fulfilled when he or she, with or without a prescription, comes to a pharmacy:

- There must be pharmacies with the ability to provide every possible pharmaceutical or pharmaceutical substance, so called full service pharmacies.
- Strict rules regarding marketing of pharmaceuticals must be in place.
- Pharmacists and prescribing doctors should have an obligation to provide information and make decisions regarding the choice of medication that are built on science and extensive experience.

To achieve a broad assortment spectrum there has to be a wide range of reliable suppliers on the national market. Ultimately it is the manufacturer or the manufacturer’s representative that decides the availability of a pharmaceutical. The pharmaceutical market is a global market and small nations
which only constitute a few parts per thousands of the total market could
have difficulties with pharmaceutical availability if the local conditions
aren’t attractive enough for the manufacturers to establish in that area.

In this aspect the pharmaceutical industry has a great responsibility for
future long-term availability of beneficial pharmaceuticals for everyone,
even if local market conditions are not always the best. Correspondingly the
conditions must be created for pharmacies to be established that will lead to
an adequate geographical distribution of pharmacy stores.

**The price must be right**

Sustainable pharmaceutical supply requires that the pharmaceutical is
reasonably priced. This means a price that does not create unreasonably
high profit margins for the pharmaceutical companies or the retailers due to
them taking advantage of the vulnerability of people with poor health. At
the same time it should be a price that covers the pharmaceutical industry’s
legitimate costs for developing the pharmaceutical, taking it through the ap-
proval process and making it commercially available.

To balance these aspects against each other is a difficult task. In most
countries there are mechanisms in place which allow the authorities use
to achieve this balance. One of these mechanisms is for the authorities to
monitor how all of the actors on the market take responsibility for pricing.
Another way is for the price of a pharmaceutical to be decided directly by
the authorities.

Factors leading to the deciding of a reasonable price may vary from country
to country. A price that is reasonable will therefore vary between countries.
It is then important that these differences in price not are used unethically
in such a way that supply is compromised in countries with low, but still
reasonable, prices.
Effective quality controls are necessary

Pharmaceuticals are one of the few groups of chemicals that we have consciously developed to be biologically active. Inherent in the definition of a pharmaceutical is that it is intended to have an effect on an individual – whether human or animal. With this there follow certain risks:

- The actual amount or concentration of active substance may not coincide with the label on the pharmaceutical package.
- The patient may use the pharmaceutical to treat a disease it is not intended for.
- The patient may take a dose that is too small or too large.
- The side effects of the pharmaceutical may be unacceptable in relation to the expected positive effect.

The consequences could be, in a worst case scenario, catastrophic. A safe and well developed quality control must therefore exist within a sustainable supply chain. As a consequence pharmaceuticals are surrounded by several restrictions. Such restrictions could be that the pharmaceuticals have to be approved by an authority in order to be allowed onto the market, that the patient can only buy a pharmaceutical if a doctor or other medical practitioner has established that the patient needs that particular pharmaceutical, that many pharmaceuticals can only be offered for sale in certain stores with special in-house competence – which today means a pharmacy.

Every pharmaceutical user should be able to be certain in the knowledge that the pharmaceutical they are about to use is of the highest quality. This results from the cooperation between manufacturers, authorities, doctors, pharmacies and users. In this aspect the distributors of the pharmaceutical have a great responsibility as they are the last link in the chain before the customer uses the pharmaceutical. Is the pharmaceutical approved for use in the way the patient intends to use it? Is the pharmaceutical that has been given to the patient the pharmaceutical that was intended by the prescribing doctor? Does the customer understand how he or she is to use the pharmaceutical? Are there any other apparent risks which make the pharmaceutical unsuitable for the patient to use?

An authorised pharmacist confirms by his or her signature on the prescription or the packaging that the pharmaceutical that has been handed over meets all of the quality requirements.
The distribution chain can be a weak link

The pharmaceutical distributor and retailer have a special responsibility to ensure that fake pharmaceutical copies cannot be sneaked in anywhere in the chain; from approved manufacturer to the retailing store. Pharmaceuticals may be expensive. Unscrupulous people might therefore be tempted to make copies or a preparation without active substance. This is especially true for patent protected pharmaceuticals. It is a big problem in many parts of the world and fake pharmaceuticals are also encountered in the West. The pharmaceutical industry collaborates with other parties in order to find a long-term sustainable system in which pharmaceutical packages are unique and identifiable throughout the entire distribution chain. In this way it will become harder to distribute fake pharmaceutical packages.

There are also other reasons for keeping the distribution chain intact. Some pharmaceuticals need to be kept cold, for example, in order not to diminish in effect and quality.

Retailers should also be responsible for determining the origin of the product and making sure that it is manufactured under acceptable working and environmental conditions. In this matter there is still much left to do for pharmaceutical retailers all over the world. So far retailers have to a large extent relied on the authority approval of the pharmaceutical, which the retailers have an obligation to be able to provide. The authorities, however, approve pharmaceuticals mainly depending on whether or not they have the medical effect they are supposed to have. Authority decisions often do not take into account aspects of sustainability, and if these are included they do not have much influence.
Inappropriate pharmaceuticals must quickly be removed from the market

In spite of rigorous quality controls, the possibility of erroneous pharmaceuticals entering the market still exists. Unexpected side effects from a pharmaceutical may sometimes also be discovered. These types of problems may have serious consequences unless distribution and usage are quickly discontinued. Retailers must therefore have access to systems for lodging complaints and for withdrawing pharmaceuticals which can be put into action quickly.

A complaint system should be rapidly able to reveal serious product errors, such as if a pharmaceutical has been erroneously labelled. The system should then rapidly notify the manufacturer and the authorities so that they can take steps to limit possible damages. Product deficiencies which are not so serious but often occur should also be caught by the complaint system. This must therefore be centralised, have fast information channels and in a systematic way be able to deal with the product, manufacturer, retailers and any others involved. In this way serious problems will be quickly discovered.

Systems for withdrawal are necessary in order to quickly remove a product from the market. The logistical information systems can directly terminate deliveries from wholesalers to pharmacists and from pharmacists to the customer. It is also possible to have the customer return the pharmaceuticals if this should turn out to be necessary. If a delivery has been made to a healthcare facility to meet an order or to a customer with a prescription the pharmaceutical is often easy to trace.

Unused pharmaceuticals constitute an environmental risk

Unused pharmaceuticals that have to be disposed of have never been of any medical benefit but may constitute a risk for the environment. Even if these pharmaceuticals may seem perfectly usable, their quality cannot be guaranteed and they should therefore not be reused. There are international regulations which declare that a pharmaceutical that has been in the possession of one customer should never be allowed back into the chain in order to be given to another customer. They should therefore be disposed of in a way that is as environmentally friendly as possible. Swedish pharmacies have for decades collected unused pharmaceuticals and sent them for incineration.
The return collection system used by the Swedish pharmacies was originally intended as a safety measure system. Unused pharmaceutical were to be prevented from falling into the wrong hands, such as those of children or drug-users, for example. Nowadays environmental reasons are motives that are as least as important for this return collection.

The pharmaceutical industry and pharmacies in Sweden commissioned polls in 2001, 2004 and 2007 in which the Swedish people were asked about their handling of unused pharmaceuticals (SIFO, 2007). These polls showed that about one third of those who received prescribed pharmaceuticals also ended up with unused pharmaceuticals. Those who answered the questionnaire knew very well that they should return unused pharmaceuticals to a pharmacy, and about 70 percent actually do so. A few dispose of their unused pharmaceuticals by flushing them down the toilet or throwing them away. The ones that do not return their unused pharmaceuticals to a pharmacy state as their reasons for this laziness and difficulties in getting to the pharmacy. Approximately 40 percent are worried about the effects pharmaceuticals may have on the environment.

During 2007 the Swedish pharmacies collected more than 1,000 tonnes of unused pharmaceuticals, including packaging material. Surveys have shown that two thirds of the packages collected had not been opened or contained at least two thirds of the original amount (Ekedahl, Wergeman & Rydberg, 2003; Ekedahl, 2003). This indicates that doctors prescribe too large amounts of pharmaceuticals and also that patients collect larger amounts than they need from the pharmacy.

There are also studies in which people who have returned pharmaceuticals to the pharmacy have been interviewed (Ekedahl, 2006). The reasons that are most often stated for returning pharmaceuticals are that the pharmaceuticals have passed their expiry date, that the patient has become healthier or has been prescribed new medication, the pharmaceuticals have not had any effect, the patient who was prescribed the medication has died or that side effects have been encountered.

In those cases where the expiry date has passed and in cases where the patient has died there is another effect that has been forgotten or not known when the pharmaceutical was returned. Studies have shown that people tend to save their medications for some time at home before returning them. Reasons for this can be concern that the disease will return and that the pharmaceutical could then be useful again or that people are not inclined to dispose of pharmaceuticals straight away if they are expensive.
There are medical as well as economical and environmental reasons for trying to minimise the amount of unused pharmaceuticals. To eliminate these completely however is not possible. We must accept that people who die will leave unused pharmaceuticals and we must be pleased when a patient becomes healthier sooner than expected when the pharmaceutical was collected from the pharmacy. Optimising the medical benefit the pharmaceutical has also leads to a reduction in the amount of unused pharmaceutical. Another area to examine in order to determine if a causal relationship exists is whether the amount pharmaceuticals disposed of can be coupled to the way the pharmaceutical is subsidised. Does a generous pharmaceutical subsidy lead to more unused pharmaceutical?

There is no completely unobjectionable, environmentally friendly and at the same time economically reasonable way by which all pharmaceuticals can be disposed of today. You have to choose whichever causes the least harm to the environment. In Sweden the discarded pharmaceuticals are incinerated under strict control. For security reasons the system is designed in such a way that there are no possibilities for any of the pharmaceuticals to go amiss. Incineration is carried out at a high temperature, the flue gases that are generated are purified and the handling of residual ash is controlled. Energy from the incineration process is also utilized in exactly the same way as the energy provided by the incineration of the combustible fraction of household waste.

Pharmaceuticals are mainly composed of organic compounds that are sometimes halogenated. Heavy metals that were previously common in pharmaceuticals, such as lead plasters and mercuric iodide are very rare exceptions today.
Looking to the future

Globalisation is taking place within the pharmaceutical area as it is within many other areas. Common regulatory systems and pharmaceutical assortments have been created within the European Union. Questions have been raised to investigate whether it would be possible to coordinate pharmaceutical subsidies and prescription regulations, for example.

Harmonisation is also happening globally. The pharmaceutical companies are to a large extent global and common quality standards are sought after. Several of the large Asian nations are now developing their healthcare to include the introduction of western knowledge, technology and products.

The probability that we will encounter a future where the medical possibilities are greater than the economical is very high. Prioritising between different public interests and creating solidarity within and between nations is going to be a challenge for future generations.

For pharmaceutical supply to become sustainable from such a point of view it has to be developed in a multifaceted way. Demographics, geography and cultural differences are examples of factors showing that superior pharmaceutical supply has to be founded on diversity, where local prerequisites and local wishes and needs have to be the guiding factors.

It is important that actors with specific interests in pharmaceutical supply, political associations and governing bodies direct future development according to long-term goals, even if that means that they have to forgo short-term economical or political gains.
References


Sustainable use of Pharmaceuticals
Åke Wennmalm, Environmental Director
Stockholm County Council
The consumption of pharmaceuticals is increasing in Sweden and in the rest of the world. When we use more pharmaceuticals the release of pharmaceutical residues from sewage treatment facilities increases and as a consequence so does the load on the environment. Why is our use of pharmaceuticals increasing? What opportunities do we have to reduce this?

There are many reasons behind our ever increasing use of pharmaceuticals. New or improved treatments and altered illness panoramas contribute to our increasing pharmaceutical consumption. There are also other factors, however, which contribute to an increased and sometimes unnecessary pharmaceutical consumption. Lifestyle, time constraints on healthcare, market forces and more people than previously refusing to put up with disease symptoms belong to this category.

If the healthy as well as the sick took a greater responsibility for their own health, this could contribute to a more reasonable consumption of pharmaceuticals. This could also happen if doctors had greater opportunities to devote time to giving information to certain patients.

Why is the use of pharmaceuticals increasing? Can we reduce usage, or at least reduce the increase?

**Even more pharmaceuticals – for even more reasons**

One reason behind the rise in the prescribing of pharmaceuticals, as previously mentioned, is that we currently have better possibilities for treating diseases where medication has not previously been available. Pharmaceutical treatment of the major widespread diseases such as cardiovascular disease, cancer, diabetes and rheumatic disease has improved considerably over the last few decades.
New diseases that require pharmaceutical treatment have emerged, such as HIV and infections involving multi-drug resistant bacteria. Other illnesses, such as depression, have increased significantly. Even for these illnesses there are better pharmaceuticals available today than was previously the case. All of this contributes to us using more pharmaceuticals than before.

This is hardly the full explanation, however, for why every Swede takes, on average, almost a full dose of two pharmaceuticals daily, year after year. Perhaps we do not accept suffering inconvenient symptoms or functional debilitation to the same extent as before. Perhaps the increased demands on our performance in our working lives and at home mean that we feel that we must be on absolutely top form all the time. Many doctors believe that elderly patients and patients in sparsely populated areas are not as quick to seek medical care as younger people and city dwellers. Can this imply that they are also less inclined to use pharmaceuticals?

**Patients are becoming more aware**

Patients today are often very well informed. The Internet enables the majority of people to find plausible diagnostic suggestions for their symptoms; but of course it must be the doctor’s clinical experience that decides.

If the diagnosis is obvious, the question of whether or not the patient requires treatment arises, and in such case, which treatment. In order to arrive at a decision the doctor takes into account factors such as gender, age, other diseases and medications, body weight, possible pregnancy, profession and social situation. It is not unusual for the patient to suggest a pharmaceutical they themselves think is suitable. There are currently clear guidelines that the doctor should arrive at a diagnosis in consultation with the patient and establish the treatment schedule in the same manner.

Often no other treatment is needed than discussion and advice. The advice can be that the patient should change their diet, their sleeping habits or lifestyle, begin to exercise or avoid contact with certain things. Sometimes a pharmaceutical is needed and can relieve symptoms over a shorter or longer period and may even cure them. In a small number of cases a pharmaceutical is essential and can be directly lifesaving.

**The easy solution**

For a number of patients the issued prescription for a pharmaceutical is the obvious conclusion to the consultation. The prescription becomes an
acknowledgement that confirms one really is sick and has not sought help unnecessarily. If the doctor does not want to write out a prescription the patient can interpret this as that he or she is not being taken seriously, or that society wants to save money on pharmaceutical costs. Such a patient can feel slighted by a decision that a pharmaceutical is not necessary.

It can be difficult for the doctor to deal with this type of patient. The demands of patients to be issued a prescription can be implicit or non-implicit and for the doctor it can be a matter of losing the trust of the patient by not prescribing a pharmaceutical. In such situations, even if the doctor is of the opinion that it is unnecessary, the prescribing of a requested pharmaceutical can be a way out. In addition the doctor often has limited time. It can be easier to hand over a prescription than to get into a long discussion with the patient about how he or she needs to change their lifestyle habits. These factors are important to remember when one analyses the reasons behind the increase in pharmaceutical consumption by 3–5 percent over recent decades.

Patients often consult more than one doctor. The reason for this can be that the patient has more than one illness, or wants to have a second opinion about their state of health. In such cases it is important that the patient informs all of the doctors about the pharmaceuticals that other doctors the patient has visited have prescribed. Otherwise there is an increased risk that the patient receives double medication for one and the same condition, or that the medications are not compatible with each other. It can also be difficult for a doctor to withdraw a treatment that another doctor has initiated.

New or improved treatments and altered illness panoramas contribute to increasing pharmaceutical consumption. Lifestyle, time constraints in healthcare, market forces and a reduction in the tolerance of many people to put up with disease symptoms can also contribute, however, to an increased and sometimes unnecessary pharmaceutical consumption.

A greater self-health responsibility, as well as the opportunity for doctors to devote more time to informing certain patients could contribute to a more reasonable consumption of pharmaceuticals.
Challenge to weigh patient benefits against environmental factors

Pharmaceuticals affect the environment to different extents. The best thing for aquatic environments is of course not to prescribe any pharmaceuticals at all. If the patient needs a pharmaceutical, however, and there are a number of alternatives, how does the doctor proceed in selecting the one that is best?

The most important is always that the patient receives a good treatment. The treatment needs of the individual patient must not be weighed against what is best for the environment and public health. On the day that the documentation about the total effect of a pharmaceutical is complete and irrefutable it may be possible for such a deliberation to be undertaken. Even then, however, it may not be evident what choice the doctor should make. Can one sum up and weigh the minor risks for the large number of people who are exposed to water contaminated with pharmaceuticals against the major risks for the small number of people who are not given their medication? The question is more ethical and moral than medical.

If there are several medically equivalent alternative pharmaceuticals it should be feasible for the patient to use the preparation that has the least impact on the environment. If one accepts this principle then the needs of the patient have been placed first and the environmental benefits have been given a secondary priority.
Within the Stockholm County Council, the combination of economic and environmental factors has been selected as a secondary priority, after the needs of the patient. This means that, if there are several medically equivalent pharmaceuticals in a particular instance, the doctor should then prescribe the preparation that has the best combined overall cost and environmental effect. If two medically equivalent preparations should differ widely in environmental effect, but only a little in cost, then the doctor should choose the one that is best for the environment and vice versa. This compromise assumes that it is possible to rationally interpret the terms major or minor cost difference and large or small environmental impact.

A system for environmentally classifying pharmaceuticals

A deliberation between environmental considerations and economic ones assumes the doctor has access to some form of environmental information concerning a specific pharmaceutical. In Sweden the pharmaceutical industry and the health service have developed a classification system for pharmaceuticals. The system specifies what environmental risk and what environmental hazard the use of a pharmaceutical can cause and is based on the fact that information about a pharmaceutical’s environmental impact is used to express risk and hazard in words, for example "slight risk of environmental effect" or "difficult to degrade in water".

Many county councils use the environmental classification as one of several instruments of selection when making their recommendations about pharmaceuticals.

This environmental classification was initiated in the autumn of 2005 with the evaluation of antibiotics and sex hormones. By the end of 2009 it is estimated that more than 60% of the bulk pharmaceuticals sold in Sweden will be environmentally classified products. All pharmaceutical groups will have been reviewed by the end of 2010.

Classification means that manufacturers suggest how each and every one of their substances should be risk and hazard evaluated. The suggestion is reviewed by an independent body – IVL, the Swedish Environmental Research Institute – that approves the evaluation, or enters into a dialogue with the manufacturer if anything is unclear. When the IVL has approved the evaluation the manufacturer can publish the result at www.fass.se. This site is open for all. Several EU countries are interested in the system.
Using environmental classification in healthcare

The environmental classification can be used in several different ways within healthcare. In Sweden, the county councils have established pharmaceutical committees that have the task of recommending which pharmaceuticals the doctor should use in the first hand when treating different diseases and conditions. These pharmaceutical committees are comprised of experienced specialist doctors and pharmacists. Healthcare services consider the advice the committees issue to be of great importance. If the committee takes the pharmaceutical’s effect on the environment into account in its work, in approximately the same manner as the Stockholm county council does, then the prescribing doctor does not need to make a judgement of their own when they choose a recommended pharmaceutical.

Another way for the doctor to take the environment into consideration is to now and again review the pharmaceuticals that he or she prescribes the most. Doctors usually memorise a certain number of pharmaceuticals that they often prescribe and they prescribe these without any auxiliary assistance, as the doctor is well aware of the package size, unit dose, dosage, side effects and how these affect other pharmaceuticals. It would be desirable for
every doctor to regularly compare their own menu of regularly used pharmaceuticals against the current list of environmentally classified pharmaceuticals and examine whether any one or more of the pharmaceuticals on their own menu should be substituted for an alternative with a lesser impact on the environment.

There still remains a need for educational efforts to raise the awareness and knowledge of doctors regarding what environmental effects pharmaceuticals have. Many of the governing bodies within healthcare to this end organise regular courses for pharmaceutical committees and for doctors who prescribe pharmaceuticals in how one should act environmentally. Other governing bodies try to limit individual pharmaceuticals that have a large environmental impact by substituting these with others that have a lesser environmental impact.

Have the efforts to environmentally adapt the prescription of pharmaceuticals been successful? Are there indications that the patterns of how doctors prescribe pharmaceuticals are changing in line with a greater environmental awareness? This question is not an easy one to answer. The assortment available on the pharmaceutical market changes from year to year. We can therefore not unequivocally explain the changes we see by the doctors consciously prescribing pharmaceuticals with a lesser impact on the environment. The research council FORMAS has devoted resources to a project to analyse which changes in the sales of pharmaceuticals are a result of environmental classification.

Different pharmaceuticals impact the environment to differing extents. Healthcare services in Sweden have developed a classification system that denotes the risks and hazards a pharmaceutical poses for the environment. Many county councils use environmental classification as one of a number of instruments for selection when they make their pharmaceutical recommendations.

If a patient needs a pharmaceutical and there are several medically equivalent alternatives, the doctor should select the preparation that has the least environmental impact.
Correct amount of pharmaceutical reduces environmental burden

Long-term treatment with a pharmaceutical that the patient has not previously taken should always be initiated with a smaller starter-pack that only contains 10–30 tablets. A larger package that lasts longer is of course easier and cheaper for the patient, but if the patient must stop taking the pharmaceutical because of side effects there are then only a few tablets to be disposed of. If the patient had directly been given a large package with several hundred tablets and was then forced to stop taking the medication there would have been significantly more tablets to be disposed of. This could have resulted in an unnecessary environmental burden.

A patient who begins a long-term treatment with a new pharmaceutical and in such case is given a starter-pack should receive compensation as the cost per tablet is more for the smaller package. Otherwise there is a risk that the patient will not begin with a starter-pack, which counteracts the aim of offering such a package. One way of doing this is by subtracting the extra costs for the starter-pack from those of the ordinary package when this is dispensed.

In Sweden it is possible to prescribe a pharmaceutical for a period of up to three months and to allow the patient to collect the medicine up to four times using the same prescription. If a pharmaceutical is prescribed for an extended duration then the risk that a portion of the pharmaceutical must be discarded increases. The doctor who prescribes the pharmaceutical should therefore always bear this in mind when writing prescriptions. If the doctor judges that a patient may have difficulty in taking their medication in the correct manner it may be prudent to give the patient their medication packaged in separate daily doses instead of in a larger package. This can be applicable for example if the patient uses several different medicines, or has dementia.

Pharmaceutical reviews are an effective tool

In recent times many hospitals and healthcare establishments have begun to introduce so called pharmaceutical reviews. The aim of the pharmaceutical review is to evaluate and update the patient’s entire medication scheme. This can be especially necessary when a patient has taken many medications over a long period of time, or when certain pharmaceuticals have been substituted for other alternatives. A further reason for a pharmaceutical review is if a patient is under the care of several different doctors.
Questions that can be addressed during a pharmaceutical review can be:

- Has the patient’s disease profile changed so that any pharmaceutical should be withdrawn or added?
- Does the patient take several medications which have similar effects – is the patient receiving double medication?
- Is the patient taking pharmaceuticals that are not compatible, or perhaps even counteract each other?

Pharmaceutical reviews have been demonstrated to be an effective tool in the improvement of the quality of healthcare. The treating doctor and nurses, a pharmacist and the actual patient, or a relative of the patient, participate in the review. The result is often that the patient receives far fewer medicines, more effective treatment and fewer side effects. It is of course also beneficial from an environmental point of view if the patient swallows fewer medicines.

Healthcare and pharmaceutical industry representatives are sometimes worried that the patients may feel a sense of guilt if the question of the negative effect of a pharmaceutical on the environment is mentioned. This concern can certainly be justified in individual cases, but with the growing interest in environmental protection issues and their importance for the welfare of future generations, the majority of patients want to know how they can contribute to reducing the stress imposed on the environment by the emissions from the community of different pollutants, including pharmaceutical residues. A rational and accurate description of the situation gives the patient the best opportunity for forming their own opinion.
Unused pharmaceuticals must be dealt with

Medicine that is unused or is past its expiry date should be returned to the pharmacy. Under no circumstances should this be thrown down the toilet or drain. The reason for this is that discarded medicine then ends up in the sewage treatment plants and these are not equipped for dealing with pharmaceutical residues in sewage water. This means that much of the pharmaceutical that arrives at a processing plant passes out into the aquatic environment. Pharmaceuticals should not be disposed of in domestic waste either. Household waste is often incinerated at relatively low temperatures and harmful by-products can be formed at such temperatures.

Therefore the only good way to get rid of unused pharmaceuticals is to return them to the pharmacy. The pharmacies then send them to a facility that incinerates the left-over pharmaceuticals at a high temperature. The emission of harmful by-products is then minimal. In Sweden there are three such incineration facilities that are approved for dealing with pharmaceuticals and it is these that receive the unused pharmaceuticals from the pharmacies and hospitals.

Following a period of pharmaceutical treatment there can often be excess medicine remaining. This can be an antibiotic course that has not been completed, pain-killer tablets that are past their expiry date or a treatment for an illness the patient no longer has. There is also often medicine remaining when an elderly patient dies.

The Swedish pharmacies have collected up and sent unused pharmaceuticals for destruction for over twenty years. Certain other countries in the EU have a similar system. From 2006 all of the member countries must have established a system for the collection of unused pharmaceuticals.

The Swedish state pharmacy Apoteket carries out regular periodical pharmaceutical polls on how compliant the Swedish population are when it comes to returning unused pharmaceuticals. In these polls it has been demonstrated that almost 90 percent of the population know that one should return old pharmaceuticals to the pharmacy.

Approximately two thirds of the population state that they also follow the instructions and return unused medicines. The most common reply among those who do not return the medicines is that these are still at home in a cupboard. A common reason for not returning medicines is the belief that the medicine might be needed in new instances of the illness.
Those who have saved unused medicine at home often return this to the pharmacy at a later date. As a result of this the state pharmacy calculates that in total approximately three quarters of all unused medicine is returned. This figure has gradually risen, which indicates that the population are returning more and more of their unused medicines.

Long-term treatment with a pharmaceutical that the patient has not previously taken should always be initiated using a starter-pack. In this way unnecessary disposal can be avoided if the patient does not tolerate the pharmaceutical.

Pharmaceutical reviews are a good way of making the patient’s medical treatment more effective. These can also contribute to reducing the environmental burden by reducing pharmaceutical use.

Expired or unused pharmaceuticals should always be returned to the pharmacy for destruction.

**Sustainable patient information – what does this mean?**

Sustainable patient information must be coupled to the patient’s abilities to assimilate it. There is a trend in modern healthcare to involve the patient more in the opinions surrounding, and intervention measures taken in regard to, their illness. There are multiple reasons for this. The age of the doctor being all-powerful and the matron ruling her ward unchallenged is over and will not return. An enlightened and informed patient is expected, through their involvement, to have better prospects for positively contributing to their own recovery. There are individual patients, however, who have difficulty in accepting the new trends. They prefer a doctor who says ”This medication will make you well” over one who says ”Clinical studies demonstrate that there is a 70 percent chance that you will get better by taking this medicine. If it doesn’t work, we will try another alternative.”

Sustainable patient information cannot be viewed in isolation, but must form part of a sustainable healthcare; and sustainable healthcare can only exist in a long-term sustainable society. With the definition we use today, however, a sustainable society is characterised as having a sustainable economy, sustainable social structure and sustainable ecology. Western society today is a long way from this kind of sustainability. Is it then possible, or even meaningful, to consider what sustainable patient information means?
What we mean today by sustainable implies that a certain system or a specific procedure can continue for an indefinite time. Regarding sustainable patient information it seems natural to give the patient free access to all of the information about their illness, but with the option for the patient not to have to know all of the information if they do not want to. A sick individual is a vulnerable person and it is hardly up to us healthy individuals to decide what the patient may want to know or not know.

Those who have a good sense of self-worth and a pronounced ability to see themselves as a part of the greater social community have the best basis for being able to accept patient information and use this in a constructive way. It would be utopian however to believe that every person in the future will have this capability. Patient information therefore becomes sustainable first when it is meaningful for the individual patient. The sustainable patient information must therefore be tailored, taking into account the recipients needs and capabilities.

Sustainable patient information about pharmaceuticals and their use can be comprised, for example, of:

- General basic facts about how a pharmaceutical works on living organisms.
- Information about the pharmaceutical’s effect and side effects.
- What the patient should do if the pharmaceutical does not have any effect, or has side effects.
- The timeframe in which the pharmaceutical should begin to have an effect in the particular situation.
- How remaining medication should be dealt with.
- If the patient should be especially cautious about anything because of the medication in question.
- If the medication can have a negative effect on the environment.
Healthy society – healthy people

A patient who has free access to all of the information concerning their disease can suffer unpleasant surprises. This is a natural consequence of coupling the majority of the responsibility for their health to the actual patient. In order to shoulder this responsibility in the best possible way the patient should be given guarantees by society regarding certain basic rights and opportunities. Among other things all people should be given equal opportunities for a safe upbringing and education, based on their interests and abilities.

It is not likely that even in a future sustainable society that all social problems will be able to be eliminated. Even in the future certain people will spend their early years in a broken home, which can result in problems during the rest of their lives. Even in the future the risks of suffering diseases of the body and soul will still be significantly greater if the formative years have been difficult.

In the future many patients will want to know significantly more than the patients of today. This applies also to what effects the pharmaceutical the patient is using has. Different patients will have different abilities, however, to take in information, even in the future. It is therefore important to make the patient information sustainable – as meaningful and useful as possible for the patient.

We must make the subsidy system environmentally friendly

A pharmaceutical costs a lot to develop and is therefore also expensive to buy. Due to this many countries have introduced official systems for subsidising costs. The objective of such systems is that people should not have to refrain from buying the medicines they need because of economic reasons. Within the EU it is the national pharmaceutical regulatory authorities that approve pharmaceuticals for sale according to those rules that have been
established by the member countries. In principle this means that a pharmaceutical that is approved for sale in one EU country also becomes approved in other member countries, even if there are certain exceptions.

When it comes to subsidising pharmaceutical costs the EU has no influence and every member country decides for itself. In the case of subsidies it is usual for the cost of a pharmaceutical to be regulated by the responsible authority in each instance.

It would be beneficial if the subsidy system was designed in a way that would stimulate the manufacturers of pharmaceuticals to develop pharmaceuticals that would degrade more easily and would not reach the environment to the same extent as today. One method could be to extend the health economics evaluation of the cost effectiveness of the pharmaceutical to include even a public health aspect. That the release of pharmaceutical residues into the environment can eventually result in health problems for the general public is one of the reasons for us wanting to have pharmaceuticals that have a lesser impact on the environment.

**Two ways to go**

There are different possibilities here. We can choose not to subsidise pharmaceuticals that have a high environmental impact. Another alternative is to make subsidies conditional so that a pharmaceutical with a low environmental impact is allowed to cost more than one with a high environmental impact.

The first alternative would mean that the company that produces a pharmaceutical that is not subsidised can charge a higher price for this. This would in all probability have the strongly negative effect that the sales in all likelihood would be small. The result would almost certainly be that the lack of subsidy would mean a negative inducement for the manufacturer. This would also mean however that the patient who needed the pharmaceutical would be forced to pay more, which is not desirable. To allow the environmental aspect to direct if a pharmaceutical should be subsidised or not is therefore hardly the way forward.

To instead allow a pharmaceutical with a low impact on the environment to cost more than a pharmaceutical with a high environmental impact would create an incentive for the manufacturer. At the same time this would mean a higher cost for the patient or for the community. By allowing a higher price to be charged for a pharmaceutical with a low environmental impact and
charging less for those with a higher environmental impact the total costs would then remain unchanged. The patient would be able to buy a pharmaceutical with a resultant high environmental impact and low cost as easily as one with a low environmental impact and higher cost and the total cost would thereby remain unchanged.

This, however, means that there is a risk that sales of the pharmaceutical that has the high environmental impact could increase because of the lower price. Certain patient groups are extremely price sensitive. For these groups the doctor must often take the cost of the pharmaceutical into consideration when he or she prescribes it. A lower price would also be able to be perceived as attractive when purchasing prescription-free pharmaceuticals, that is to say when the actual patient chooses the product. Differential pricing with respect to the degree to which the pharmaceutical impacts the environment must therefore be carefully evaluated.

Sweden and several other EU countries have introduced a system for substitution when it comes to subsidised prescription pharmaceuticals. The objective is that it should then be possible to substitute one pharmaceutical for another that has an equivalent effect but is cheaper. In Sweden a pharmaceutical can only be substituted for another product that contains the same active substance. In certain countries, however, it is possible to change to a product with a different active substance. In these cases it would be desirable if changing to another substance that has a larger impact on the environment was not allowed.
A Swedish example

In Sweden it is the state Dental and Pharmaceutical Benefits Agency TLV (Tandvårds- och läkemedelsförmånsverket), who were previously called LFN (Läkemedelsförmånsnämnden), who determine if a pharmaceutical should be entitled to be subsidised or not. TLV make their judgement based on three different principles:

- The human worth principle – that all people are of equal worth and therefore should have equal rights to support.
- The requirement and solidarity principle – it is the patient’s needs and the severity of the disease that determines if a pharmaceutical should be subsidised.
- The cost effectiveness principle – how effective the treatment is in relation to other treatments and to the severity of the disease.

If TLV decide that a pharmaceutical should have the right to be supported and therefore subsidised then the authority also determine the price that the manufacturer is allowed to charge when the pharmaceutical is sold at the pharmacy. The subsidy benefits the patient through the so called high-cost protection register, which means that no single person currently needs to pay more than 1 800 Swedish kronor per year for their pharmaceuticals. All of the costs in excess of this are covered by the county council registered as the patient’s home county. The county councils have the majority of their pharmaceutical costs refunded by the state.

In the preparatory work before the establishment of TLV the possibility of taking into account the environmental impact of a pharmaceutical when assessing if it should be entitled to be subsidised or not was discussed. To date this has not come into being for different reasons. To introduce some form of public health or environmental assessment into the analysis of cost effectiveness could be a possible avenue for the Swedish system for subsidies to promote pharmaceuticals with a lower environmental impact.
Many countries subsidise pharmaceuticals so that patients do not refrain from taking the pharmaceutical because it is too expensive.

It would be beneficial if the system for subsidy encouraged the manufacturers to develop future pharmaceuticals so that they had a lesser effect on the environment than the pharmaceuticals available today. The practice of substituting one pharmaceutical for another equivalent pharmaceutical at the pharmacy should not be allowed if this imposes a greater load on the environment.

Patients who begin their medical treatment with a starter-pack should not be forced to pay more for this, but should instead receive compensation to cover the excess charge via the subsidy system.
Pharmaceuticals in the Environment: Knowing and Managing the Risks

Klaus Kümmerer, Professor, Department of Environmental Health Sciences, University Medical Centre Freiburg, Germany.
How do we deal with the contamination of the environment by pharmaceuticals? There are not only single pharmaceutical chemicals to consider, but also their breakdown products, mixtures of different pharmaceuticals, biopharmaceuticals and diagnostic reagents. Furthermore, other, non pharmaceutical chemicals can be present and interact with the latter. We have to consider issues such as the possibility of unforeseen effects and effects greater or lesser than that of the original pharmaceutical administered. How do we reduce contamination? What specific purification processes are there, and how do we implement them?

Nowadays we know for certain that pharmaceuticals are present in the environment. Their presence in the environment is part of a more general micro-pollutants problem. The significance of metabolites and transformation products is not known. In developed countries concentrations measured for pharmaceuticals in the environment are more or less in the same range. It is not clear, however, whether this holds for less developed countries too.

There are no short term effects on humans. However, the risks of active pharmaceutical ingredients, or APIs, remain poorly understood. Long term effects cannot be ruled out with knowledge at its present state. Risk assessments do not explicitly take into account elderly people and the unborn. Effects on environmental organisms may happen. Effects of mixtures are not included in risk assessments. Awareness of the presence of pharmaceuticals in the environment, coupled with evidence of effects, however, suggest that precautionary management action to reduce the release of pharmaceuticals to the environment should be considered.

As for effluent treatment, no technology works well for all compounds. Advanced effluent treatment is not sustainable because of energy consumption, efficiency end efficacy.
Therefore, its appropriateness must be assessed on a case by case basis. Measures at the source, such as handling and use, are necessary in the long run, as are improvements in the active pharmaceutical ingredients themselves, such as more biodegradable pharmaceuticals.

**A success story and a danger**

The history of the pharmaceutical sciences is an impressive success story. Pharmaceutical industry products are present everywhere in every day life. They help to pursue the modern way of living. They contribute to our health and high living standards. Heavy pollution of the environment and serious health effects have however been associated for a long time with the production of chemicals and pharmaceuticals, their usage and application.

During the second half of the last century tremendous progress was made to prevent the pollution of the environment and to reduce the impact of such pollution on health. Nowadays proper and effective treatment and prevention of emissions into air, water and soil is in place in developed countries and will make its way to all places on the globe. Since the end of the last century, however, it has also been learned that the products of the pharmaceutical industries themselves, i.e. the pharmaceuticals, can present a new type of environmental pollution and a possible health risk to the consumer.

The ever increasing performance of analytical instruments has revealed that active pharmaceutical ingredients or APIs, like other micro-pollutants (Schwarzenbach et al., 2007), are present in the environment at low concentrations (ng/l–μg/l). These molecules end up in the environment not because of improper use but, on the contrary, by their proper use. If the APIs, their metabolites and transformation products are not eliminated during sewage treatment, they may enter the aquatic environment and eventually reach drinking water and the presence of pharmaceuticals in the environment is today a widely accepted fact.

Despite pharmaceuticals in the environment being a relatively young topic a vast amount of literature has already been published on the subject. In the beginning research was focussed on the analysis and presence of pollutants (Kümmerer 2001). Later, research into their fates and (eco)toxic effects came into foreground (Kümmerer 2004a). Nowadays risk assessment and risk management issues are gaining momentum (Kümmerer 2008a). In this chapter a very brief overview of current knowledge will be given and some research issues will be addressed.
Active pharmaceutical ingredients – what they are

From a chemical point of view active pharmaceutical ingredients cover a wide range of small molecules with different physico-chemical and biological properties. Even minor changes in the chemical structure of an API may have a significant impact on its environmental fate (Cunningham, 2008) and separate assessments can therefore be necessary for each type of API.

Some medicines contain molecules based on proteins, so called biopharmaceuticals. Biopharmaceuticals are medical drugs produced using biotechnology by means other than direct extraction from a non-engineered biological source. Examples are proteins including antibodies, and nucleic acids or recombinant human insulin. Their environmental relevance is not yet clear and they are not yet a focus of environmental research and risk management. Some researchers argue that biopharmaceuticals should have no environmental impact because they should degrade fast because of their natural origin. However, structurally related compounds such as plasmids have been found in the environment. Furthermore, it is known that the prions that are protein structures are very stable. A prion (proteinaceous infectious particle, -on by analogy to virion) is an infectious agent composed only of protein. They cause a number of diseases in a variety of animals and Creutzfeldt-Jakob disease (CJD) in humans. Prions are believed to infect and propagate by refolding abnormally into a structure which is able to convert normal molecules of the protein into the abnormally structured form. This altered structure renders them quite resistant to denaturation by chemical treatments and physical agents,(proteases, heat, radiation and formalin) making disposal and containment of these particles difficult (see en.wikipedia.org/wiki/Prion). This demonstrates that knowledge about the significance of biopharmaceuticals in the environment is by far too little for any conclusions.

Other groups of compounds that are of interest and that are used in medical environments are disinfectants and diagnostics such as X-ray contrast media or contrast media used in magnetic resonance imaging, MRI. In addition to the active substances, medicines may contain additional chemicals such as pigments and dyes or plasticizers or inorganic components. The latter are often of minor importance for the environment. However, it is known that e.g. plasticizers have endocrine disrupting activity.
Parent Compounds and their offspring

Pharmaceuticals can be classified according to their purpose and biological activity, like antibiotics, analgesics and anti-neoplastics. Classification according to chemical structure is used mainly for the active pharmaceutical ingredients within sub-groups of medicines, for example within the group of antibiotics or the subgroups within the antibiotics such as β-lactams, cephalosporins, penicillins or quinolones. Other classifications refer to the mode of action, such as anti-metabolites or alkylating agents within the group of cytotoxics and anti-neoplastics. In case of classification according to the mode of action, chemical structures of molecules within the same group can be very different and therefore their environmental fate can be different too.

Many pharmaceuticals undergo a structural change in the body of humans and animals, respectively. The result of such a process is metabolites. After their excretion and introduction into the environment, both parent compounds and metabolites can undergo structural changes by a variety of biotic and non-biotic processes. Pharmaceuticals can be incompletely transformed by organisms such as bacteria and fungi in the environment (Haß and Kümmerer, 2006; Gröning et al., 2007; Trautwein et al., 2008) as well as by light and other abiotic chemical processes.

Structural transformations may also be a result of technical processes such as advanced effluent treatment by oxidation and photolysis (Ravina et al., 2002; Zühlke et al., 2004; Li et al., 2008b; Méndez-Arriaga et al., 2008). The resulting molecules are called transformation products (Längin et al., 2008 and figure 1). Such structural changes result in new chemical entities with new properties.

Normally, it is assumed that metabolism and transformation of active pharmaceutical ingredients leads to decreased toxicity. In some cases however, metabolism leads to more active compounds, for example in the case of prodrugs. The same has been found for photolysis and other oxidizing processes.
There are many sources for APIs

The APIs used in medicine as well as the additional compounds in medical formulations may enter the environment by different routes. These include several different non point sources such as manufacturing plants, effluent from sewage treatment plants, waste and landfill effluent.

Usually, it is assumed that emissions from manufacturing and production are low in Europe and the North Americas. It has been found only recently in Norway however that the input from a local manufacturer was much higher for a certain antibiotic than inputs originating from hospitals and the general public (Thomas, 2008). Only recently it has been found that in Asian countries concentrations up to several mg/l of active pharmaceutical ingredients can be found in effluents from manufacturing plants (Larsson et al., 2007; Li et al., 2008a,b).
These results demonstrate the need for more data. Data concerning emissions during transport and storage would also be beneficial to collect.

As expected, pharmaceuticals are present in hospital wastewater (Steger-Hartmann et al., 1997; Hartmann et al., 1996; Kümmerer, 2001; Gómez et al., 2006; Brown et al., 2006; Seifrtová et al., 2008; Schuster et al., 2008). Concentrations of pharmaceuticals in hospital wastewater are higher than in municipal sewage. The total substance flow is, however, much lower than that related to municipal wastewater. This is because of the much lower share of usage of pharmaceuticals in hospitals compared to the general public effluent in developed countries (Schuster et al., 2008; Thomas, 2008). Occasional data from Sweden indicate that the pharmaceutical panorama in hospital wastewater differs in composition rather than in concentration in comparison to municipal water in general (Wennmalm, personal communication). Dilution of hospital wastewater by municipal wastewater is in excess of a factor of 100 (Kümmerer and Helmers, 2000). In other words, hospitals are a minor source. Separate treatment of hospital wastewater may therefore be questionable, but reduction of active pharmaceutical ingredients in hospital effluent, for example by proper use, is still an option (see below).

In accordance with the new EU-legislation, all member states shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired (EG, 2004). If the collected products are incinerated this is probably the most effective and environmentally sound way to handle the problem. If the waste is landfilled the active pharmaceutical ingredients will show up after some years in the effluent of the landfill (Eckel et al., 1993; Holm et al., 1995; Ahel and Jeličič, 2001; Metzger, 2004). If there is no collection of the effluent this may be a source for the contamination of surface water or ground water.

It has been found that people violate the current EU legislation by discarding remaining and out-of-date pills and liquid pharmaceuticals into the toilet (Götz and Keil, 2007; www.start-project.de; Bound and Voulvoulis, 2005; Seehusen and Edwards, 2006; Abahussain et al., 2006; Ruhyo and Daughton, 2007). These findings suggest that there is a role for patient education about the proper disposal of unused and expired medications in all countries. In several countries systems for returning unused medications have been in place since several years (see Nequille and Bugnon, 2008). In Sweden follow-up studies of patient compliance indicate that around 90 % of all inhabitants know that unused or expired pharmaceuticals should be returned to the pharmacy, and that about 70 % in fact do so (Gunnarsson, personal communication).
Occurrence and fate in the environment

There is currently evidence of the occurrence of some 160–180 different active pharmaceutical ingredients in the aquatic environment. For more we do not yet have the appropriate analytical methods. APIs have been found in the effluent from medical care units, municipal sewage and the effluent of sewage treatment plants, in surface water, sea water, ground water and in drinking water (Heberer, 2002; Kümmerer, 2001, 2004a, 2008a,b). Seasonal variations have been studied in sewage and reclaimed waste as well as in finished water (Loraine and Pettigrove, 2006; Alexy et al., 2006). Pharmaceuticals have also been detected in the effluent from landfill sites. They are also detected in the arctic environment (Kallenborn et al., 2008). The concentrations of pharmaceuticals in surface water and the effluent from sewage treatment plants have been shown to lie in the ng/l to μg/l range.

Recently the presence of psycho-active and illicit drugs have been detected in surface water and wastewater (Zuccato et al., 2005; Boleda et al., 2007; Huerta-Fontela et al., 2008; Castiglioni et al., 2008). These include amphetamines, cocaine and its metabolite benzoylecgonine, morphine, 6-acetylmorphine, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, methadone and its main metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine. Despite the fact that knowledge of pharmaceuticals in sewage sludge and biosolids is necessary for the proper understanding of fate and for risk assessment, only little knowledge is available (Jones-Lepp and Stevens, 2007).

Little is known about the occurrence, fate and activity of metabolites. An important question to be addressed is whether glucoronides, methylates, glycinites, acetylmates and sulfates are still active and whether they can be cleaved by bacteria during sewage treatment and in the environment.
This would result in the active compound being set free again. Other types of metabolites are also excreted and can be detected in wastewater (Miao et al., 2005). Their effects on environmental organisms may be lower than that of the parent compound. In the case of pro-drugs, however, the situation is probably different. This may also be the case for the metabolites of several other pharmaceuticals, as has been shown for example for norfluoxetin (Nalecz-Jawecki 2007).

**Processes for removal**

The predominant fate processes for the removal of pharmaceuticals in and from the different environmental compartments are (bio)degradation and adsorption. The latter is important for example for tetracyclines and quinolones (Golet et al. 2002). Photo-degradation and hydrolysis can also be significant in surface waters and technical treatment processes.

Sorption may have an impact on the spread (particle bound transport) and bioavailability of pharmaceuticals in the environment. Binding to particles or the formation of complexes may cause a loss in detectability, as well as a loss in activity. Adsorbing APIs may diffuse into bio-films, be present in sewage pipes, sludge flocks or on stones in rivers and lakes. This may result in a biased risk estimate, as concentration in such “reservoirs” may be much higher than in the free water phase. The effects and behavior of antibiotics in such bio-solids with high bacterial density and special conditions has not yet been investigated. Knowledge about these issues is very little. Even much less is known about the conjugates, other metabolites and transformation products in this respect.

Bacteria and fungi are the two groups of organisms that are best able to degrade organic compounds. Fungi are particularly important in soils, but they do not usually play an important role in the aquatic environment. In sewage treatment plants, surface, ground and sea water bacteria are therefore assumed to be responsible for most biodegradation processes. The rate and degree of biodegradation of active pharmaceutical ingredients in sewage treatment and the aquatic environment depend on the type and number of microorganisms present and the API itself. The presence of pharmaceuticals in the aquatic environment demonstrates at least incomplete degradation and elimination in sewage treatment.
**Effects are in many cases unknown**

The risks posed to humans from pharmaceuticals in the environment seem to concern environmental hygiene rather than toxicology and pharmacology. The maximum possible intake with contaminated water within a life span – calculated at 2 litres drinking water per day over 70 years – is far below the dosages used in therapy. This statement relies however on the following assumptions:

i) That effects and side effects during short term, high dosage therapeutic use are the same in quality and quantity as during the long term and low dosage of a life long ingestion.

ii) That the effects are the same for foetuses, babies, children, healthy adults and elderly people.

iii) That the risk imposed by a single compound is comparable to that imposed by a mixture.

How to extrapolate data from high dose short term ingestion during therapy to a the low dose and long term ingestion of “medication” via drinking water, is still an unresolved issue in toxicology – and in ecotoxicology.

Information available on the effects of active substances on organisms in the aquatic and terrestrial environment is increasing but is still too little (Fent *et al.*, 2006). Effects on daphnia, algae and bacteria have been demonstrated using low concentrations in chronic tests (Holten Lützhöft *et al.*, 1999; Yamashita *et al.*, 2006). For diclofenac, effect concentration for fish toxicity was in the range of wastewater concentrations (Schwaiger *et al.*, 2004; Triebskorn *et al.*, 2004, 2005; Hoeger *et al.*, 2007), whereas the effect thresholds of propranolol and fluoxetine for zooplankton and benthic organisms were near to maximal measured sewage treatment plant effluent concentrations (Fent *et al.* 2006).

In surface water, concentrations are lower and so are the environmental risks. Targeted ecotoxicological studies are, however, lacking almost entirely and such investigations are needed, focusing on subtle environmental effects (Fent *et al.*, 2006).
Mixtures may have different effects

All risk assessment is based on single compounds. It has been observed, however, that mixtures might exhibit different effects than that of single compounds (Silva et al. 2002, Pomati et al. 2008). Additionally, it has been found that standardized tests may underestimate the effects (Kümmerer et al., 2004).

It has also been found that detrimental effects may occur if compounds are transferred within the food web. In the years spanning 2000 and 2003, for example, high annual adult and sub-adult mortality, 5–86 percent, of the oriental white-backed vulture, with resulting population declines of 34–95 percent, were associated with renal failure and visceral gout. A direct correlation was found with residues of the anti-inflammatory drug diclofenac and renal failure. Diclofenac residues and renal disease were reproduced experimentally in oriental white-backed vultures by direct oral exposure and through feeding diclofenac-treated livestock to the vultures (Oaks et al. 2004). Evidence from studies strongly implicates mortality caused by ingestion of residues of the veterinary non-steroidal anti-inflammatory drug diclofenac as the major cause of the decline. Other findings show that veterinary use of diclofenac is likely to have been the major cause of the rapid vulture population declines across the subcontinent (Swan et al., 2006; Taggart et al., 2007).
Use antibiotics with prudence

Antibiotics are one of the most important groups of active pharmaceutical ingredients used in medicine. Unwanted effects of microbial growth have long been controlled through the use of antimicrobials such as antibiotics. Bacteria resistant to antibiotics have been found in the aquatic environment (Kümmerer, 2004b; Watkinson et al., 2007; Kim and Aga, 2007; Schlüter et al., 2007; Caplin et al., 2008). In general, the emergence of resistance is a highly complex process that is not yet fully understood with respect to the significance of the interaction of bacterial populations and antibiotics, even in a medicinal environment. Is the input of antibiotics into the environment an important factor for the emergence of resistant bacteria in the environment? Or is the transfer of resistance from already resistant bacteria following improper use of antibiotics much more important than the input of the antibiotic compounds themselves?

The link between the presence of antimicrobials and the bias towards resistant bacteria is not yet established, nor are the transfer of resistance at concentrations as low as those found for antimicrobials in the environment. Knowledge of sub-inhibitory concentrations of antimicrobials and their effects on environmental bacteria is scarce and contradictory, especially with respect to resistance (for details see Kümmerer, 2004b,c). In any case, prudent use of antibiotics is crucial for the avoidance of resistance.

Understanding risks and managing them

Information on long term risk of active pharmaceutical ingredients is missing in most cases, while the acute effects are quite comprehensively documented. Data allowing for a sound risk assessment for metabolites and transformation products are missing more or less completely. Furthermore, up to now risk assessments have been undertaken for single substances only and not for mixtures. Some of the active pharmaceutical ingredients have carcinogenic, mutagenic or reproductive toxic effects, so called CMR-compounds. It is unclear how such compounds should be treated (Kümmerer et al., 2008).

Besides toxicity, the issue of persistence is of particular importance for the assessment of the environmental significance of substances. Persistent organic pollutants increase the potential for long-term and hence varied effects. The longer the exposure lasts, 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, 1992).
Combinations of management strategies will be likely to be the most effective in mitigating the risks presented by pharmaceuticals. Strategies such as advanced effluent treatment, pharmaceutical-return programs and incentives for the development of “green” pharmaceuticals (Kümmerer 2007) are needed for an effective reduction of the input of pharmaceuticals and other chemicals into the environment.

The strategy that has been most extensively discussed within recent years is advanced effluent treatment. In order to implement pharmaceutical-return programs we have to learn that environmental protection has to include the shareholders, the stakeholders and the people using the compounds. This means educating patients, doctors, nurses and pharmacists when seeking solutions that will work. The third strategy is emerging from the field of green chemistry. In terms of sustainability it seems to be the most promising one in the long run.

**Specific advanced effluent treatment options**

The advanced treatment of effluents has been investigated using photo-chemical 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) and constructed wetlands (Matamoros and Bayona, 2006). 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).

It has been found that each type of advanced effluent treatment has its specific limitations and in general some severe drawbacks (Jones et al., 2007; Wenzel et al., 2008; Kümmerer, 2008d). Mutagenic and toxic properties have been found for example for reaction products of photooxidation processes (Isidori et al., 2005, 2007, Wei-Hsiang and Young, 2008; Méndez-Arriaga et al., 2008; Calza et al., 2008). Therefore, advanced effluent treatment should not be considered as a general solution to the problem. Instead it should be considered only as a part of the solution on a case by case basis. Contributions by hospitals to the total load of pharmaceuticals in municipal wastewater are for most compounds below 10 percent. For the majority of compounds this figure is mostly even below 3 percent (Kümmerer and Henninger, 2003; Heberer and Feldmann, 2005; Bayerisches Landesamt für Umwelt, 2005; Heinzmann et al., 2006; Thomas et al., 2007; Thomas, 2008; Schuster et al., 2008).
Therefore, in contrast to common assumptions it is questionable whether separate treatment of hospital effluent is a valid environmental and economic goal.

**Reducing the impact of left-over drugs**

A major unknown with respect to drugs as pollutants is what fractions of drug residues occurring in the ambient environment result from the discarding of leftover drugs (Götz and Keil, 2007; Ruhoy and Daughton, 2007). Properly informing doctors, pharmacists and patients could contribute to the reduction of the input of active pharmaceutical ingredients into the aquatic environment. Furthermore, data is required on the types, quantities and frequencies with which drugs accumulate in households, hospitals, retirement homes and rehabilitation hospitals (Ruhoy and Daughton, 2007).

In a mid- to long-term perspective, prescription, therapy and consultation practices of physicians and pharmacists, as well as the patients’ use and disposal patterns of pharmaceuticals should be changed towards a higher environmental sensibility. The relationship between physicians and patients plays a key role within this strategy. Knowledge and information about the environmental relevance of pharmaceuticals heightens the problem awareness of physicians in patient consultations.

In order to facilitate the integration of the problem into the physicians’ everyday practice, it has to be introduced into medical education and advanced training an implemented by those responsible for education and health policy. Health funds can foster the demand for ecological alternatives by means of changes in the funding of pharmaceuticals and therapies. This increased demand can support the pharmaceutical industry in supplying a sustainable product range, for example varieties of packaging sizes and potencies.

If an internal hospital commission recommends a positive list of recommendable pharmaceuticals that form the basis for purchasing activities, the variety of products is reduced and savings will result. The wards should not be allowed too much storage space. This would reduce the share of outdated medicaments and consequently the environmental burden. The internal system should allow the wards to return in-date opened but not yet used packages to the pharmacy. The pharmacist can handle these remainders properly. A medical doctor who is a specialist in infectious diseases should be available to give advice on the proper use of antibiotics. Proper hygiene, that is not too much, not to little, at the right place and time can also contribute to
minimizing infections and the need for pharmaceuticals and disinfectants.

**Benign by design**

According to the principles of green chemistry, the functionality of a chemical should not only include the properties of a chemical necessary for its application, but also easy and fast degradability after its use. Taking into account the full lifecycle of pharmaceuticals will lead to a different understanding of the necessary functionality for a pharmaceutical (Kümmerer, 2008d).

In current discussions, improvements in synthesis are very prominent, whereas the environmental properties of the molecules are somewhat underestimated. Applying these principles and the 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 – the pharmaceuticals are “benign by design”.

Such an approach is not completely new. It is quite common, for example, during the development of pharmaceuticals with respect to unwanted side effects. This can also result in economical advantages in the long run and will fit with green pharmacy (Daughton, 2003; Kümmerer, 2007).

Contributions of the different stakeholders to risk management are summarized in Table 1 (Kümmerer, 2008a).
Table 1. Opportunities to reduce the input of pharmaceuticals into the environment (Kümmerer 2008a)

<table>
<thead>
<tr>
<th>Who</th>
<th>Possible Measures and Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Science</td>
<td>Move on green and sustainable pharmacy. Establish criteria for the quality of data necessary for risk assessment and risk management together with the pharmaceutical companies and regulators.</td>
</tr>
<tr>
<td>Pharmaceutical companies</td>
<td>Publish data relevant for environmental assessment. Publish analytical methods and results. Offering suitable package sizes. Integrate environmental aspects in the development of new active pharmaceutical ingredients and new therapies, including environmental properties, dedication to green pharmacy, less over the counter products. Establish take back systems where not already in place. Properly inform doctors, pharmacists and the general public. A new understanding and promotion of shareholder value that includes the sustainability of products.</td>
</tr>
<tr>
<td>Wholesaler</td>
<td>Deliver not only pharmaceuticals but also proper information.</td>
</tr>
<tr>
<td>Patients</td>
<td>Improve compliance. Use active pharmaceutical ingredients only if necessary and only after prescription by a medical doctor. Don’t wash outdated medicaments down the drain; instead return these to the pharmacy if there is a take back system established, or into the household waste if appropriate (check with local authorities and pharmacies). Don’t use so called life style drugs. Use alternative treatments such as acupuncture for anti-pain treatment.</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>Inform patients and doctors. Participate in take back systems if appropriate (check with local authorities).</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Integrate the delivering pharmacy/wholesaler into the handling of outdated medicaments. Inform doctors and patients. Establish proper procurement. Apply the Swedish classification system (<a href="http://www.fass.se">www.fass.se</a>).</td>
</tr>
<tr>
<td>Medical doctors</td>
<td>Prescribe according to environmental criteria if alternatives are available. Apply the Swedish classification system (<a href="http://www.fass.se">www.fass.se</a>). Inform patients.</td>
</tr>
<tr>
<td>Health Insurances</td>
<td>Keep the necessary medical standards and demonstrate the reduction potential and economical benefits. Inform doctors and patients. Apply the Swedish classification system (<a href="http://www.fass.se">www.fass.se</a>).</td>
</tr>
<tr>
<td>Wastewater handling and treatment</td>
<td>Reducing input by broken sewerage or piping. Reducing total water flow to be treated by separate piping of wastewater and rain water, thereby increasing the concentration of APIs. Apply affordable technologies. Develop less water and energy demanding treatment systems and technologies. Proof of appropriateness of advanced treatment on a case by case basis.</td>
</tr>
<tr>
<td>Drinking water treatment</td>
<td>Extend monitoring. Use advanced treatment if necessary. Inform the general public.</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Who</th>
<th>Possible Measures and Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authorities</td>
<td>Initiate and back up communication between all stakeholders. Develop limits and thresholds for APIs in different environmental compartments and drinking water. Establish country adapted classification systems for pharmaceuticals as already in place in Sweden.</td>
</tr>
<tr>
<td>Banks</td>
<td>Include sustainability in rating of pharmaceutical companies.</td>
</tr>
<tr>
<td>Politics</td>
<td>Include APIs in environmental legislation. More restrictive connection between environmental properties and authorization of human pharmaceuticals. Improve legislation for the management of outdated medicaments. Establish incentives for the development of greener drugs, for example a prolonged patent lifetime.</td>
</tr>
</tbody>
</table>
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Feminized Fish and Vulnerable Vultures - Pharmaceuticals as Environmental Pollutants Require Novel Testing Approaches

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Current ecotoxicological risk assessments procedures fail to fully address the fact that pharmaceuticals are generally not toxic in a conventional sense. Examples of pharmaceuticals causing changes to the behaviour of fish are known. Such changes can be as lethal to an animal as any poison. The dangers to ecological systems from pharmaceuticals affecting specific biological pathways in non-target organisms must be further examined. Several methods are today being developed to study this, for instance within the framework of the MistraPharma research programme.

The history of environmental chemical pollution comprises a still growing list of man-made chemicals unintentionally ending up in the aquatic environment and biota. This is mainly because wide-spread use, resistance to degradation and potential for bioaccumulation lead to low-level long-term exposure in the environment. Active pharmaceutical ingredients are a group of compounds that must be added to the list of potentially hazardous chemicals that end up in the aquatic environment. To date almost 200 pharmaceutical substances have been identified in surface waters.

The existence of active pharmaceutical ingredients in surface waters is certainly a cause for concern, but existence is only one prerequisite for there being a risk to the environment. Evidence of harm is the other. Relatively little is known today about the probability of harm associated with the occurrence of these compounds in the environment (see the chapter by Kümmerer), but the fact that the great majority of these compounds are designed for potent interactions with biological systems, and that these biological systems in many cases are similar in humans and in aquatic organisms significantly adds to the concern. The risk to aquatic species cannot easily be dismissed.
Dealing with the danger — environmental risk assessment

In order to determine whether a contaminant constitutes an environmental risk or not, a risk assessment has to be performed. The main purpose of an environmental risk assessment is to estimate the probability and severity of harm. This in turn provides sufficient information for decision-making with the purpose of protecting the ecosystem from unwanted effects.

Environmental risk assessment is generally performed by establishing a ratio between a Predicted Environmental Concentration of a contaminant (denoted PEC) and a concentration where no harm to relevant organisms is expected, i.e. the Predicted No-Effect Concentration (denoted PNEC), or in other words, data on exposures are compared to data on toxicity. The higher the expected environmental concentration is compared to concentrations that are considered to be safe, i.e. the higher the ratio, the more concern would be raised.

In Europe the development towards a legislation requiring environmental risk assessments for pharmaceuticals began in the early 1990s, and guidelines on this subject was finalized only recently (EMEA 2006). European legislation now requires a pre-marketing environmental risk assessment for new active pharmaceutical ingredients. The aim is to identify risks that these compounds may pose to the aquatic environment. If such a risk is identified, the aim is furthermore to provide measures for the reduction of environmental exposures (EU 2001). A similar legislation exists in the United States (US FDA 1998) and is also under development in Japan, Canada and other regions.

Documented environmental effects

So far, only very few active pharmaceutical ingredients have been conclusively shown to cause adverse effects in organisms in the environment. During the 1990s, and at the beginning of this decade, a series of reports together provided convincing scientific evidence that environmental exposure to steroidal estrogens, including ethinylestradiol from birth control pills, caused harm to the reproductive systems in wild fish (Purdom et al., 1994, Desbrow et al., 1998, Routhledge et al., 1998; Larsson et al., 1999; Jobling et al., 2002; Thorpe et al., 2003; Parrot and Blunt, 2005; Kidd et al. 2007). The reason this cause and effect relationship could be scientifically established in the field was that estrogens give rise to very specific morphological changes in the sex organs of male fish (feminization including ovotestes, hermaphroditic gonads containing both testicular and ovarian tissue). Induction of a specific,
and easily measured biomarker for estrogenicity (vitellogenin induction) was furthermore demonstrated in fish caged downstream from wastewater treatment plants.

Another example where substantial evidence exists for an environmental impact of drugs is the case with the dramatically declining vulture populations in India and Pakistan (Oaks et al., 2004; Green et al., 2004). Vultures feed on dead cattle. In India and Pakistan cattle are frequently given diclofenac, an anti-inflammatory agent commonly used in both veterinary and human medicine. The residues of diclofenac in the cattle meat has proven to be highly toxic to the kidneys of the vultures, leading to gout and eventual death.

**Generating knowledge about ecotoxicity**

To make a reasonably robust environmental risk assessment, a significant amount of relevant data of sufficient quality is needed. The European legislation requiring environmental risk assessment for pharmaceuticals was implemented only recently. Since the legislation requires environmental risk assessment only for newly developed pharmaceuticals, there is still a severe scarcity of environmental data. Ecotoxicity data are publicly available for little more than one hundred pharmaceuticals and only a handful of substances can be considered well-investigated with respect to their effects in environmental organisms.
Laboratory as a model

If a proactive risk assessment is aimed for, then evaluations have to be performed before the environment has been contaminated. Consequently the Predicted No-Effect-Concentration has to be based on data obtained from laboratory experiments. The major advantage of this approach is that all factors influencing the model can be kept under strictly controlled conditions. But the laboratory experiments consider only a fraction of the whole environment. In most cases the experiments focus on identifying effects after exposure to single substances and in one species at the time. The environment, on the other hand consists of millions of species, with different morphology, physiology, and behaviour, living under a large variety of ecological conditions. The species are therefore also affected also by a number of different abiotic factors (temperature, sunlight, availability of oxygen, exposure to different contaminants etc.). The environment, in other words, is a complex web of biotic and abiotic interactions, and organisms in the environment are continuously exposed to a myriad of influences. In such complex systems, cause and effect relationships can be very difficult to identify. There are simply too many factors coming into play, many of which are interrelated in different ways.
The laboratory is therefore used as a model of the environment. We know that this is not a perfect model, but there is a general consensus that this approach can generate meaningful knowledge that will help predict environmental risks. So, to achieve a scientifically well-motivated environmental risk assessment a combination of experimentally derived toxicity data and data on actual or calculated exposure levels are needed. However, these data should, when possible, be supplemented with data from field studies.

The standard ecotoxicity tests currently in regulatory use for pharmaceuticals were mainly designed to identify unspecific toxicity of industrial chemicals. The chemicals that for regulatory purposes are categorized as “industrial chemicals” include substances that are used in an uncountable number of industrial and other applications. Consequently they differ widely in their chemical properties such as reactivity, volatility, solubility in water and fat, and other characteristics. Factors that determine the chemicals’ fate in the environment and their potential for interacting with biological systems.

In contrast to industrial chemicals active pharmaceutical substances are deliberately designed to interact potently with a specific biological target, such as a receptor protein. This interaction is fine-tuned to affect a particular biological process and to have as few other effects or side effects as possible.

**Focusing on the pharmacological mode-of-action**

It is a reasonable hypothesis that pharmaceuticals have the potential to cause responses that relate to the pharmacological pathways that they are designed to affect also in non-target organisms. Such interactions are particularly plausible if a protein similar to the human drug target protein is present in the species of concern. Consider for instance the following example: Medicines acting as antidepressants are designed to affect the human central nervous system (CNS) in very specific ways. If another species, such as a fish is exposed to an antidepressant and the molecular target for the drug in the fish is sufficiently similar to that of humans, then it can be expected that exposure to a sufficiently high concentration of the drug will lead to an altered CNS function also in the fish.

This can then be manifest as altered behaviour of the fish. Such alterations could for instance affect the capacity of the fish to find and kill prey, or affect its capacity to find a partner and mate. In these cases the final outcome of the exposure would be increased mortality of the exposed fish. This outcome is thus not related to the pharmaceutical being “toxic” in the traditional sense, but to biological alterations caused by the intended pharmacological
mechanism of the drug. The final result for the fish would however be similar; the probability of survival would be reduced (e.g. Perreault et al. 2003, Gaworecki and Klaine 2008)

Well conserved targets

Ecotoxicity testing of general industrial chemicals aims at covering a broad range of possible types of (unspecific) adverse effects. Testing of pharmaceuticals, on the other hand, should primarily focus on identifying effects related to the intended pharmacological mode of action. (e.g. Länge and Dietrich, 2002; Dzialowski et al., 2006). Such a directed approach to testing is motivated by the fact that many pharmacological targets exploited in human and veterinary medicine are evolutionary old and consequently conserved through evolution. This means that many targets of pharmaceuticals are similar across species. For example, the primary target protein for the drug simvastatin is HMG-CoA-reductase, the rate limiting enzyme in the cholesterol biosynthesis. This enzyme is functionally well conserved in many types of organisms, from yeast to humans. Accordingly, simvastatin and other statins acting via HMG-CoA-reductase, potently affect organisms as distantly related as humans, crustaceans and yeast. (Dahl et al., 2006, Gunnarsson et al., 2008)

Improved knowledge about the evolutionary history of drug-targets and their functions across species could be important for the process of identifying sensitive and relevant test species. This is instrumental for developing improved strategies for risk identification (Ankley et al. 2007, Gunnarsson et al., 2008; Kostich and Lazorchak, 2008; Seiler, 2002; Lubick, 2008).

The pre-marketing data requirements for the active pharmaceutical substances are extensive. Candidate pharmaceuticals undergo testing using a number of different experimental models with the purpose of demonstrating the effectiveness of the drug in interacting with the intended biological target, and to identify potential adverse effects and toxicity. Such testing is required by law and has to be performed before a drug may be used in a clinical trial and ultimately be marketed. The required testing includes sufficient documentation of therapeutic effects, characterization of modes of pharmacological action, general toxicity testing, and when relevant, long-term reproductive and carcinogenicity testing.

Developing improved test systems for demonstrating ecotoxicity of pharmaceuticals thus includes taking the extensive knowledge about their primary pharmacological action into account. It should also consider the evolution
of biological target molecules and their physiological function in potential test organisms. Together this can generate hypotheses about which effects should be expected.

**Exploratory testing**

That different organisms have drug targets in common and are thus prone to be affected by the same types of pharmaceuticals, does not automatically imply that the same effects are consistently observed across species. The physiological function of a specific drug target and its downstream pathways may differ between species to a greater or lesser extent. It is also possible that proteins that are not considered important targets in humans may show high affinity for a specific drug in a non-target species. To enable the identification of a wider range of responses, and to search for unanticipated effects, directed testing approaches need to be supplemented with more exploratory testing methods.

Using exploratory techniques, a large number of alterations are studied simultaneously within each assay. This provides the means for investigating a very broad range of changes and thus has the potential to discover unexpected effects.
Examples of such exploratory methods are microarray-, proteomic- and metabolomic methods that can identify how a living organism responds to pharmaceuticals at the molecular level. These so-called “toxicogenomics” methods analyse changes in the abundances of genetic responses (levels of mRNAs), amounts of certain proteins or small metabolites. We can then identify the genes that are regulated, and the proteins and metabolites that are affected by being exposed to the pharmaceuticals. Together, such information can assist in pinpointing disturbed physiological processes.

Another exploratory methodology is histological analysis. Histological analyses comprise a detailed microscopic examination of tissues and organs to identify changes in their structure caused by exposure to a particular substance. This is also an “open” or exploratory approach in the sense that various effects on tissue-structure can be determined. The histological approach could be particularly useful in studies aiming to demonstrate effects on development, sex differentiation and reproductive organ function following early life-stage exposure in aquatic vertebrates.

When the exploratory test reveal that a particular substance has the potential to cause harm in the test organisms at concentrations relevant to those measured in the aquatic environment, the next step will be to determine the relationship between the observed histological, physiological or molecular response and an adverse chronic outcome affecting development, growth, reproduction or survival of the test species.
Relating effects to exposures

As previously described, an environmental risk assessment requires knowledge about both effects and exposures. Exposure data can be obtained either by direct measurements or by using model calculations, or a combination of these methods.

Huggett et al. (2003, 2005) presented a simple approach – the “fish plasma model” – to predict if a given water concentration of an active pharmaceutical ingredient is likely to cause a physiological response in exposed fish. The model compares a theoretically estimated fish plasma concentration with a known human or mammalian therapeutic plasma concentration (Huggett et al. 2003).

The fish plasma model relies on:

i. the availability of knowledge about the concentration in blood plasma that will give rise to the intended primary pharmacological effect in human subjects (or occasionally in another species), and
ii. that the molecular drug target is expressed and functionally active in the wildlife species of interest (in this case the fish).

The basis of the fish plasma model is that we assume that a conserved drug target will be affected at roughly the same blood plasma concentration of the drug in both species. One of the novelties with this approach is that it could be used to theoretically screen a very broad range of pharmaceutical substances. The information from such a screening could provide important clues for identifying substances that could pose a threat to the aquatic environment and thereby guide further research.

Apart from being important to protect from an environmental perspective, the chosen model organism was fish because the physiology of fish generally is remarkably similar to that of humans, particularly at the molecular level, such as drug target molecules (Evans, 1993; Gunnarsson et al., 2008). In the cases where the target protein is not present in the fish, or is not sufficiently similar to the mammalian counterpart, the fish will be less sensitive and the fish plasma model might overestimate the actual risk. However, as a screening tool used to identify risky substances in a tiered approach, some overestimations of risk can be accepted. These will be corrected later in the process, when actual testing is performed.
Effect ratios expose potential risk pollutants

The model proposed by Hugget et al. provides an equation that yields effect ratios (ER). The effect ratio is the ratio between the plasma concentrations of humans who have received a therapeutic dosage of the pharmaceutical and the plasma concentration in fish (see Equation 1).

\[
ER = \frac{HTPC}{F_{ss}PC}
\]

Equation 1. ER = effect ratio, HTPC = Human therapeutic plasma concentration, F_{ss}PC = Fish steady state plasma concentration.

If the effect ratio < 1 then the concentration in the exposed fish is higher or equal to the known concentration that gives rise to a pharmacological response in humans. It should be emphasized that this model only estimates the probability of a pharmacological effect and not whether this effect is adverse or not. Some pharmacological effects might have no identifiable influence, while others will be harmful to the exposed organism.

Data on human therapeutic plasma concentrations (HTPC) are found in literature in the public domain. How to accurately predict a steady state plasma concentration (F_{ss}PC) in fish is a much more open question. A very simplified method, proposed by Hugget et al., is to base the prediction solely on the octanol-water partition coefficient (log P) of the pharmaceutical and its concentration in the water. Either a measured environmental concentration (MEC) or a predicted environmental concentration (PEC) calculated based on for example sales statistics, can be used. Since the octanol-water partition coefficient can often be accurately predicted, it is possible to estimate a theoretical fish steady state plasma concentration (F_{ss}PC) even for pharmaceuticals that lack an experimentally established log P.

Although the fish plasma model is a promising screening tool, there is still significant uncertainty about how well we can predict bioconcentrations of pharmaceuticals from water to fish plasma. The generation of actual bioconcentration data for a large number of pharmaceutical substances is instrumental for the assessment of this general model and for refining it.
The MistraPharma approach

The fish plasma model is one of the starting points of the research programme MistraPharma. Within this programme effect ratios have been calculated for all of the pharmaceuticals on the Swedish market with three general exceptions; (1) all the pharmaceuticals that the European Medical Agency (EMEA) has exempted from environmental risk assessment requirements, i.e. vitamins minerals, vaccines, etc, (2) pharmaceuticals that lack a determined human therapeutic plasma concentration, i.e. certain ophthalmologic agents, some substances applied topically etc., and (3) antibiotics. Antibiotics were not included due to the different approaches needed to study the environmental impact of these pharmaceuticals.

Theoretical effect ratios based on predicted environmental concentrations were therefore calculated for 789 pharmaceutical substances. Preliminary data analysis shows that 121 of these have an effect ratio below 1000 (Fick et al., unpublished), which is the suggested uncertainty margin to take into account differences in sensitivity between species and other uncertainties (Huggett et al., 2003).

Who are the suspects among the pharmaceuticals?

Among the 121 pharmaceuticals identified as having an effect ratio below 1000 are for example, ethinylestradiol (ER = 1.1) and several other sex hormones, angiotensin II antagonists, as well as several anti-psychotic and anti-depressant pharmaceutical substances (Fick et al., unpublished).

Experiments have now started to compare theoretically derived effect ratios with empirically measured ratios. Previous studies on a limited number of pharmaceuticals suggest that the simplistic model for bioconcentration used here in several cases predicts the effect ratio fairly well, but also that there is room for significant improvement in the model (Hugget et al., 2003, Brown et al., 2007; Fick et al., unpublished).

Based on these data, MistraPharma researchers will select a number of pharmaceutical substances for testing, using both exploratory and mode-of-action-based ecotoxicological test methods as described above. Pharmaceuticals identified as high risk substances will furthermore undergo traditional testing including long-term and reproductive toxicity tests.
Concluding remarks

It seems likely that other classes of pharmaceutical substances than estrogentic hormones and diclofenac could also give rise to adverse effects in the environment. It seems also likely that other organisms than those already investigated can be affected by exposures to pharmaceutical substances. It has for instance just recently been shown in laboratory experiments that exposure to ethinylestradiol can cause sex reversal in frogs at environmentally relevant concentrations (Pettersson and Berg 2007; Gyllenhammar et al. 2008). During the past few years more data have been gathered, mainly from laboratory studies, suggesting that a range of pharmaceutical substances could have different types of effects on wildlife at concentrations reported in sewage effluents or surface waters (Fent et al. 2006). Recent reports of the release of high levels of antibiotics in effluents from certain drug manufacturers are also special cases where there is no doubt that the environment is severely affected (Larsson et al., 2007; Li et al., 2008; Larsson 2008; Carlsson et al., 2009).

Improving current methods for risk identification for pharmaceuticals in the aquatic environment is a challenging task. A major obstacle is the limited amount of data currently available regarding the potential adverse effects that these compounds may cause to aquatic species. This could be solved by revising the legislation and introducing requirements for further testing. Current ecotoxicological test methods have however not been developed to identify the specific effects that may be the result of exposure to substances with very diverse and yet specific modes-of-action, such as pharmaceuticals. The development of new experimental methods has to rely on extensive research efforts and the MistraPharma research programme is one significant initiative towards this aim. To standardize novel test methods so that they can become internationally accepted test guidelines is another very time and resource consuming process. It requires cooperation between scientists and regulators across nations and jurisdictions. The possibility to establish effects following low environmental exposure concentrations will however be severely restricted until new and suitable test methods have been established.

Pharmaceuticals are chemicals of vital importance for human health, but at the same time they are increasingly recognized as potential environmental pollutants. Because of their importance to human well-being, it is usually not possible to refrain from their use. The risk reduction options are thus either limited to using less hazardous alternatives if available, or to using downstream risk management options such as improved wastewater treatment. The MistraPharma research programme also aims at improving wastewater
treatment technologies (see the chapter 9 by La Cour Jansen and Ledin). To avoid unnecessary costs for risk reduction, an iterative process integrating knowledge about environmental risk with the development of improved technologies for risk mitigation is necessary. The combined efforts along these lines have the potential to generate solutions that are scientifically motivated, as well as technically and economically feasible. A sustainable use of pharmaceuticals includes ensuring that the ecosystem is protected from unwanted effects caused by these substances. To achieve this will require cooperation between the pharmaceutical industry, the regulatory agencies, the healthcare services and the scientific community.
MistraPharma is a Swedish research programme funded by the Swedish Foundation for Strategic Environmental Research (Mistra). The main purposes of the programme are to:

Identify pharmaceuticals that constitute a significant environmental risk. MistraPharma will consider all 1200 active pharmaceutical ingredients currently available on the Swedish market. This is so far a uniquely comprehensive approach.

Recommend techniques to improve wastewater treatment technologies. MistraPharma will define, evaluate and develop promising methods for removal of high risk pharmaceuticals through wastewater treatment. Improve risk identification strategies.

Propose improved test strategies for environmental risk identification. Strengthen the contacts and the communication within the Swedish and international network of scientists and stakeholders.

The MistraPharma programme has been developed, and will continue to work, in close cooperation with stakeholders and the end-users of the research.

For further information see www.mistrapharma.se
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Jes la Cour Jansen and Anna Ledin
MistraPharma
Today specific methods are about to be developed and tested that potentially will be able to remove pharmaceutical residues from wastewater. The best method to apply for removal of one pharmaceutical compound can, however, be completely different from the most suitable method to remove another. There is no single simple solution that can be applied to solve the overall problem. With improvements in the methods available for detecting pharmaceutical residues and their concentrations the questions of actual needs and cost justification need to be addressed.

Human consumption of pharmaceuticals predominantly takes place at home, in hospitals or at other medical centres. Production facilities only contribute a significant discharge into the environment in special cases. Figure 1 shows the primary pathways from use and disposal to degradation or disposal on land or discharge to surface waters. The trend today is that more and more medications are taken at home, where the remnants, after usage, end up in the toilet and go into the sewage system. Sewage systems and the wastewater treatment plants consequently have the potential to be an efficient barrier for protecting the environment against threats from the use of pharmaceuticals.
Pharmaceuticals in the urban water and waste system

Today’s modern wastewater treatment systems are built for collection and transportation of wastewater. They are also built to reduce organic matter that may cause oxygen depletion in the recipient surface water and aim to reduce nutrients (nitrogen and phosphorus) that can cause over-fertilisation of recipient lakes, streams and the sea. The major problem related to an excessive nutrient load in surface water bodies is the excessive algal blooms that cause unpleasant smells and oxygen depletion when the algae sinks to the bottom and degrades.

The present knowledge is rather weak regarding the practical experience of removal or degradation of pharmaceuticals at wastewater treatment plants. First of all, good analytical procedures have only been established for a limited number of substances. Analytical procedures for particle bound substances in particular are lacking.
What has been identified and quantified until now has more been a question of the analysis methods available than of real evaluation and prioritising of problematic substances or evaluation of the potential for removal at the treatment plants. In addition, the combination of the removal potential for a promising supplementary method and the present combinations of removal processes at the treatment plants have only been taken into consideration to a limited extent.

**Fate of the pharmaceuticals**

When pharmaceuticals, or the remains of pharmaceuticals after use, enter the wastewater system they follow the water and enter the wastewater treatment plants where their fate is governed by the physical, chemical and biological properties of the substance and of the treatment processes in use at the treatment plant.

The treatment plants of today are not designed for the reduction/degradation of pharmaceuticals. The fate of the pharmaceuticals in the plants is therefore determined by the character of the substance itself and of the processes used at particular plants. In some cases the pharmaceuticals can be biologically degraded, if the process conditions are favourable at the plant. *Figure 2* shows the fate and degradation/reduction mechanisms of pharmaceuticals in a modern wastewater treatment plant.

![Figure 2. Fate and degradation/reduction mechanisms of pharmaceuticals in a modern wastewater treatment plant.](image-url)
Three main mechanisms have to be taken into account in order to understand the fate of the substances in wastewater treatment systems.

- Evaporation of volatile compounds
- Compounds ability to adhere to particles
- Solubility of the pharmaceuticals in water

These three mechanisms determine the pathways in the treatment systems and the possible degradation/separation of the pharmaceuticals in the treatment plant. They are also very significant for the final fate of the substances.

What is known today is that very few pharmaceuticals are volatile. This means that evaporation from the plants is not significant. Some, but not many, pharmaceuticals bind strongly to the sludge and are handled at the sludge treatment parts of the plants. The majority of substances are water soluble and will pass through the plants, unless they are degraded.

The pharmaceuticals present in the sludge are only expected to be degraded to a minor extent. The major methods for handling sludge today are anaerobic digestion, with no further treatment before disposal on agricultural soil, utilisation as soil conditioner or incineration. Anaerobic digestion is carried out to reduce the volume of sludge to be handled, for biogas production and for reduction of pathogens.

Destruction of pharmaceuticals by anaerobic digestion has been demonstrated in a few cases. However, it is assumed that the anaerobic conditions in the process are not suitable for degrading the chemical structures of most abundant pharmaceuticals. Incineration means complete destruction of the pharmaceuticals whereas the other solutions mean that the pharmaceuticals reach the soil environment.

The consequence of the above is that most of the pharmaceuticals have to be handled in the water treatment part of the treatment plants. This is the focus of the following section.

**Water treatment**

Degradation of pharmaceuticals depends, as mentioned above, on the processes in use at the wastewater treatment plant and on the chemical structure of the substance.
Some pharmaceuticals e.g. some contrast media are almost biologically undegradable while other substances have been found to be more or less degradable under existing treatment conditions. The parameter known as solid retention time (or sludge age) lies at the heart of the efficiency of the degradation. Increasing the time means that more types of slow growing bacteria are present and increases the likelihood that some bacteria can degrade a given pharmaceutical if it is present.

*Figure 3* shows removal results for Ibuprofen (IBP) and Bezafibrate (BZF), from a number of treatment plants (Clara *et al.* 2005). Results are shown as a function of the solid retention time (sludge age) in the system. This parameter indicates the length of time the degrading bacteria require to do their job. It can be seen that as long as the sludge is treated for a long time (it has a high sludge age) the Ibuprofen is almost completely removed. The picture for Bezafibrate is a bit more complicated with a tendency towards increased removal with increased solid retention time, but other phenomena also play a role in this case.

![Figure 3](image-url). Removal results for Ibuprofen (IBP) and Bezafibrate (BZF), from a number of treatment plants (Clara *et al.* 2005). Results are shown as a function of the solid retention time (sludge age) in the system.
The sludge age phenomena is especially important in relation to Sweden as more than 100 treatment plants for treatment of wastewater from more than 10,000 people have a short sludge age. Removal at these plants is therefore assumed to be limited.

The methods used in Sweden exhibit a clear geographical distribution and distribution according to the size of the plants. The most advanced biological treatment with nitrogen and phosphorus removal is required south of a line from the Norrtälje municipality, at the Baltic coast, to the Hagfors municipality, at the Norwegian border (~ latitude 60°). There the temperature in the wastewater treatment plants is high enough for advanced biological treatment all the year around.

Only the smaller plants and a few in the interior of the country have combined chemical and biological treatment only, without nitrogen removal, south of this line. North of the line the large plants typically have combined chemical and biological treatment, whereas most of the smaller plants only have mechanical and chemical treatment.

*Figure 4* shows the typical process schemes for wastewater treatment plants in the northern and southern parts of Sweden. The processes are indicated and the expected removal of organic matter as suspended solids and BOD (indicates the amount of biologically degradable substances in the water) are given together with reduction of phosphorus and nitrogen. It is seen that the plant volumes required are very different and that the plants in the south where a long sludge age are used in order to obtain nitrogen removal are significantly larger than the northern ones.
Figure 4. Typical process schemes for biological wastewater treatment plants in the northern and southern parts of Sweden. In the tables the expected removal of suspended solids (SS) and organic matter as BOD (indicates the amount of biologically degradable substances in the water) are given together with reduction of phosphorus and nitrogen if the biological treatment is combined with chemical precipitation of phosphorus.

**Promising new methods**

The search for improved treatment efficiency is a question of finding solutions to suit the most environmentally significant pharmaceuticals, quantifying the reduction of these in existing treatment plants and then utilizing the new and promising treatment methods, which can be combined with the present ones, to secure the necessary removal.

A number of different new treatment technologies need to be evaluated. The most environmentally significant pharmaceuticals might not have been identified yet and it is anticipated that among these a number of different substances with rather different chemical properties will be identified that are necessary to remove. As the treatment needs to take place at existing facilities with very different processes and ability to remove pharmaceuticals today, the methods need to be tailored to almost each individual plant or group of plants with similar process schemes.
There has to be a corresponding balance between the need for removal of only a few out of the many pharmaceuticals, the varying degrees of reduction at existing treatment plants and the potential for removal/destruction of pharmaceuticals with methods that are specialised for the purpose. If all pharmaceuticals have to be removed to as great an extent as possible, the implementation of several new methods would be required, which would probably be expensive, but would also have potentially high energy and other environmental costs.

The new methods take as their starting point the chemical properties of pharmaceuticals. Since some substances can be adsorbed to a surface the possibility for implementation of adsorbents in the process scheme has to be included. Furthermore, methods to separate particles with adsorbed pharmaceuticals needs to be evaluated.

As some substances are not biologically degradable, chemical treatment needs to be evaluated for destruction of the substance, or for partial degradation of the structures, in order to facilitate biological treatment.

Finally biological methods have to be evaluated and optimised. Only then can we find the optimal strategy between continuing with the present operation, the possibilities of optimising this sufficiently, or of combining the existing solutions with new ones.

It is expected that technologies based on most of the principles above may play a role in Sweden because of the significant variation in the destruction mechanisms of pharmaceuticals and the varying existing wastewater treatment technology.
Physical methods

Physical methods imply only separation from the wastewater with no destruction of pharmaceuticals. This means that methods for handling the separated substances need to be included in the evaluation. Physical methods can be optimised to remove almost all particles but without any destruction of the pharmaceuticals. Besides the removal of the pharmaceuticals all other particles and substances adsorbed to particles are removed. That means in general an improved removal of many other substances from the wastewater, such as particulate organic matter, nitrogen and phosphorus, heavy metals and also pathogens. The problem related to physical methods is that the substances end up in the sludge or in a concentrated stream that needs further handling.

Different kinds of filters (sand filters, disc filters, membrane, micro and ultra filters) are traditionally used for particle removal. Removal of particles removes only the fraction of the pharmaceuticals that are bound to the particles, which in most cases is a minor fraction. However it might be more important to remove particles as an optimal pre-treatment before applying e.g. chemical and biological treatment methods, as particle removal could increase the effectiveness and the economy of these methods.

Membranes with very small pore sizes, such as membranes for reverse osmosis, nanofiltration and ultrafiltration, can be used for direct removal of some pharmaceuticals. Since the molecular weight of most pharmaceuticals lies within a narrow span (around 100-1000 g/mol) it is assumed that direct removal of pharmaceuticals based on membranes is a possible (but expensive) solution in case of the need for removal of a very broad spectrum of substances.

Several types of materials that easily accumulate pharmaceutical compounds on their surfaces – adsorbents – such as activated carbon, minerals and molecular imprinted polymers, have characteristics that make them interesting to use for removing pharmaceuticals. While there are relevant adsorbents with activity for most pharmaceuticals the problem with using them is that the full adsorption capacity cannot be exploited due to fouling of the materials and loss of adsorption capacity because of binding by other organic molecules present in treated sewage. Activated carbon and minerals are relevant for a broader spectrum of active pharmaceutical ingredients, whereas molecular imprinted polymers may fit uniquely if a very limited number of problematic pharmaceuticals are identified as potentially harmful to the environment.
Chemical methods

The chemical methods presented here result in the destruction of substances other than pharmaceuticals as they are quite unspecific. Industrial chemicals and other refractory substances will be degraded in parallel to the pharmaceuticals, which in general will lead to improved effluent quality. Further, the oxidation methods result in destruction of most of the bacteria, which can give improved hygienic effluent quality. A problem that needs special attention is the risk of generating new biologically active substances.

Chemical methods result in complete or partial destruction of the pharmaceuticals. Complete destruction where the substance is converted into carbon dioxide and water is generally expensive whereas partial destruction may lead to improved biological degradability afterwards. Partial destruction can lead to the formation of new substances, which are normally less harmful than the original chemical. Examples exist however where newly formed degradation products are more harmful than the parent compound. Degradation experiments with Carbamazepine have shown the formation of several transformation products including acridine and acrodone. Acrodone is one example of a compound that have non-wanted biological effects of greater importance then the mother compound since it is known to cause DNA damage and exhibits greater ecotoxicity (Encarnación and Arce, 2007; Wiegman et al., 2003).

Chemical degradation based on advanced oxidation processes (e.g. Vacuum-UV, UV/H2O2, H2O2/O3 and UV/O3) and selective oxidation reagents (ClO2, MnO4− and O3) can be used to oxidise pharmaceuticals, typically as a post treatment after traditional treatment of the wastewater. Using this treatment pharmaceuticals generally lose their pharmaceutical potency and become more easily biodegradable. Selective reagents can be used for removal of a very broad spectrum of active pharmaceutical ingredients and advanced oxidation processes might be the solution in cases where a complete oxidation of organic material is necessary to destroy pharmaceuticals that are difficult to remove with other methods.

Biological methods

Improved biological methods can be applied for the biological degradation of a broad spectrum of pharmaceuticals. Traditional biological wastewater treatment has, as shown above, been used to partially remove/degrade some pharmaceuticals and degradation may be enhanced by increasing the sludge age in existing biological treatment or by polishing of the effluent in
new processes tailor made for that purpose. A more radical option is to use membrane bioreactors for removal of the active pharmaceutical ingredients by extended biodegradation. This treatment is advantageous compared to traditional activated sludge systems or trickling filters as the treatment can be performed using an extreme sludge age, which increases the biodegradation of normally non degradable pharmaceuticals.

**Added benefits and problems**

Besides the direct process-related benefits and problems there are a large number of additional side effects typically included in an Environmental Impact Assessment. These are e.g. the size of the facilities needed, the need for new infrastructure, transport, use of chemicals and energy demands amongst other factors. In addition some of the methods may impact on the safety and health of the workers at the treatment plants. In conclusion, all the methods have significant costs associated with their implementation. It has been calculated that the cost for wastewater treatment will increase 20–100% if some of the more advanced methods have to be implemented.
Summary

The present wastewater systems in Sweden are at a high technological level. Introduction of new methods at the existing treatment plants has been done before as the development in environmental awareness has been the driving force for the technological improvements for decades. Reduction of pharmaceuticals however is a great task since the treatment methods needed for the different substances is strongly varying. Implementation to reasonable economical and environmental costs needs a strong prioritizing system so the pharmaceuticals that course the environmental risks are the ones that determine the selection of methods.
References


Legal Requirements for Sustainable Development
Bettina Rechenberg
German EPA
There are differences between the environmental assessments carried out prior to approval of a new pharmaceutical based on whether it is for human or veterinary use. Are these existing procedures adequate, or is there a need to review existing legislation? New initiatives for reducing environmental pharmaceutical contamination may be necessary.

For more than 20 years, European legislation has required an environmental risk assessment within the pharmaceutical authorization procedure. Authorisation of a human medicinal product, however, can explicitly not be denied if an environmental risk is identified. For veterinary pharmaceuticals the legal situation is different - authorisation may be denied, or may be limited to certain application areas, if evidence for an environmental risk exists. Guidance documents describing the data and test results necessary for environmental risk assessments were accepted in 2001 and 2005 respectively for veterinary pharmaceuticals and in 2006 for human medicinal products. Are these requirements sufficient to guarantee a sustainable use of pharmaceuticals? Or are additional measures necessary to avoid negative effects of drugs in the environment and to contribute to a sustainable development in general?

The EU Environmental Assessment Legislation for Pharmaceuticals

The elaboration of EU documents on the environmental risk assessment of human and veterinary pharmaceuticals began more than two decades ago. This was established with the EC Directives 81/851/EEC and 93/39/EEC respectively. These have been replaced by the new codified Directives 2001/83/EC (EC 2001a) for human medicines and 2001/82/EC (EC 2001b) for veterinary medicines; each consolidating a number of older Directives relating to the authorisation of pharmaceuticals. These Directives were again amended by the EC Directives 2004/27/EC (EC 2004a) and 2004/28/EC (EC 2004b) (Koschorreck, de Knecht 2004).

“a marketing authorization in one Member State ought to be recognized by the competent authority of the other Member States unless there are serious grounds for supposing that the authorization of the veterinary medicinal product concerned may present a risk to human or animal health, or to the environment (recital 7). The environmental impact should be studied and consideration should be given on a case-by-case basis to specific provisions seeking to limit (recital 23).”

The risk/benefit balance includes

“any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health and any risk of undesirable effects on the environment” (Article 1(19)).

Furthermore

“reasons for any precautionary and safety measures to be taken when storing the veterinary medicinal product, administering it to animals and disposing of waste, together with an indication of potential risks that the veterinary medicinal product might pose to the environment, to human and animal health and to plants…” and “results of tests assessing the potential risks posed by the medicinal product for the environment shall be submitted” (Article 12).

Compared to the Directive 2001/82/EC, the Directive 2001/83/EC (as amended) regulating the authorisation of human pharmaceuticals addresses the environment to a much lesser extent:

“The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged. In any event this impact should not constitute a criterion for refusal of a marketing Authorization (recital 18). The application shall be accompanied by, if applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment” (Article 8(g)).

This means that even if an environmental risk is identified, authorisation of a human medicinal product can explicitly not be denied, but for veterinary pharmaceuticals authorisation may be denied or limited to certain application areas if evidence for an environmental risk exists.
Guidance document on the environmental risk assessment of medicinal products

The risk assessment procedure is divided into two phases: phase I, which is a drug environmental concentration estimation, and phase II, which is an assessment of physical, chemical and ecotoxicological properties. In addition, an exposure threshold value or “action limit” separates the exposure estimation in the first phase from the test requirements in the subsequent second phase. The goals of the risk assessment include protection of the aquatic and terrestrial ecosystems, groundwater, micro-organisms in sewage treatment plants and top predators.

The assessment considers environmental exposure from the use of the medicinal product only. An assessment of the environmental risk arising from the drug production and/or the disposal of used or unused pharmaceuticals is outside of the scope of the guidance documents.

All guidance documents describe a two phased and logically tiered approach. The exposure calculation, the action limits in Phase I and II and the data requirements are however different according to the specific environmental exposure of human pharmaceuticals and veterinary pharmaceuticals, respectively.
Environmental risk assessment for human medicinal products

The guidance document for human pharmaceuticals came into force in 2006 (EMEA 2006).

In Phase I, the drug concentration expected to occur in the aquatic environment is calculated based on the maximum daily dose. If this value (PECSURFACEWATER) 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 to the environment. The assessment procedure does not then continue. If however the calculated concentration in surface water exceeds the action limit of 0.01μg/l a Phase II environmental fate and effect analysis is required.
When known effects from related substances or results from biological studies indicate an unusually high risk of ecotoxic effects (e.g., potential endocrine disruptors), then a Phase II assessment should be carried out irrespective of the predicted environmental concentration. Furthermore, a screening for persistence, bioaccumulation, and toxicity is necessary if the n-octanol-water partition coefficient (log Kow) exceeds 4.5. This identifies a potential risk for bioaccumulation (Figure 1).

**Figure 1. Environmental Risk Assessment of Human Medicinal Products**

Natural substances like vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, and herbal medicinal products are exempted from environmental assessments.

In the second phase, information on the physical, chemical, and ecotoxicological properties is obtained and assessed in relation to the extent of the environmental exposure. Phase II is split into two tiers, Tier A and Tier B.

A screening information base data set in Tier A starting with chronic effects data allows for a rapid prediction of the environmental risk for the aquatic compartment (algae, daphnia, fish) and for microorganisms. Additional assessment criteria are the potential transfer to sediment, adsorption to sludge and transfer to terrestrial ecosystems with sludge spreading, as well as bioconcentration potential.

If no risk is identified at the Tier A level, the assessment is considered completed. Conversely, if a risk is identified at the Tier A level, then an extended ecotoxicity data set is required to be submitted at the subsequent Tier B level (Koschorreck, de Knecht 2004).
Since the EMEA guideline came into force, dossier quality is improving and, full risk assessment data set submissions are increasing. These data will be used for a revision of the guideline (review of the action limit, suitability of tests). A first analysis of the data shows that less than 10% of all synthetic pharmaceutical ingredients are readily biodegradable.

In the USA a guidance document for human pharmaceuticals came into force already in 1998 (FDA 1998). The environmental risk assessment starts with a worst case exposure calculation, based on the yearly production volume of the active ingredient. If the estimated concentration of the substance in the aquatic environment is going to be 1 μg/l or greater, then experimental data are required. The Guideline document describes multi-tiered data requirements during Phase II, starting with acute effects data.

**Environmental risk assessment of veterinary medicinal products**

In 1996 the European Agency for the Evaluation of Medicinal Products (EMEA) adapted a comprehensive Note for Guidance to assist the applicant in the evaluation of the environmental risk assessment for veterinary medicinal products. In order to achieve harmonisation between Europe, USA, Japan, Canada and Australia/New Zealand on the data requirements for registration of veterinary drugs, the Steering Committee of the International Cooperation on the Harmonisation of data requirements for the authorisation of veterinary medicinal products (VICH SC) in 1996 authorized the formation of a working group to develop new phase I and II guidelines for environmental risk assessment.

The guidance document on Phase I was finalized on 15th June 2000 and implemented in 2001 (VICH 2000), and the guidance document on Phase II in 2005 (VICH 2005). On the basis of these two documents a more detailed Technical Guidance Document was drawn up for Europe and came into force in 2007 (EMEA 2007).

Similar to the first phase of the environment risk assessment of human pharmaceuticals, Phase I identifies veterinary medicinal products that require a more extensive investigation of their potential environmental effects on non-target organisms. In Phase I, the investigator shall assess the potential extent of exposure to the environment from the product, its active substances and other ingredients. The assessment has to take into account the target species, the proposed pattern of use, characteristics of the constituents...
of the veterinary pharmaceutical and the method of administration. In Phase I several exemptions from further testing are incorporated, e.g. physiological substances such as vitamins, electrolytes, natural amino acids and herbs. Products intended for administration to companion animals (not including horses) are also exempted.

Phase I is further divided into assessments of drugs used in the aquatic and terrestrial branches respectively. With respect to the aquatic branch, any veterinary medicinal product intended for use in open systems are forwarded to Phase II. In cases where the environmental introduction concentration of the remaining pharmaceutical (equivalent to the concentration in the effluent) released from aquaculture facilities is less than 1 μg/l, the exposure levels are considered irrelevant. Otherwise, a Phase II assessment is required. With regard to the terrestrial branch, drugs that are endo- and ectoparasiticides used in pasture will be advanced to Phase II, because these medicinal products are pharmacologically active against organisms that are biologically related to pasture invertebrates. For other pharmaceuticals, Phase I assessment is considered complete if the predicted environmental concentration in soil is less than 100 μg/kg (Figure 2).

The Phase II assessment starts at Tier A with a base data set on fate and behaviour in soil, water and dung, and on effects on aquatic and terrestrial organisms. This allows risk characterisation. If a risk cannot be excluded, the assessment proceeds to Tier B and requires an extended ecotoxicity data set (Koschorreck, de Knecht 2004).

![Figure 2. Environmental Risk Assessment of Veterinary Medicinal Products](image)
Risk mitigation measures within the authorization procedure

If refinement in Tier B confirms that the medicinal product presents a risk to the environment, then the applicant is expected to propose appropriate precautionary and safety measures for the use of the medicinal product. Such mitigation measures are included in the Summary of Products Characteristics (SPC) and the Package Leaflet (PL).

Risk reduction measures for veterinary drugs based on environmental safety concerns are quite common. According to the EC Directive 2001/83/EC as amended however, risk mitigation measures for human pharmaceuticals must not reduce the availability of the medicine. The risk mitigation measures used for veterinary pharmaceuticals or for pesticides can not therefore be applied to human medicines. Veterinary pharmaceutical risk mitigation measures are also inapplicable because of the regional and chronic exposure to human drugs from a large number of point sources. Measures beyond those regulating drug authorization are necessary.
Because obligations to collate environmentally relevant data were introduced into the authorization procedure only a few years ago, there are still significant data gaps regarding impacts on the environment for many pharmaceuticals which have been on the market for a long time. In particular, there is a lack of information regarding ecotoxicity analyses and chronic effects. For many frequently and intensively used active substances, it is currently impossible to perform a substance risk assessment regarding the consequences of pharmaceutical discharge into the environment. Given the marketing intensity of many products and the proven persistence and widespread presence of certain pharmaceutical substances in the environment, this imbalance in the basic data situation is unacceptable. Based on similar programmes for existing chemicals or pesticides, a European programme for “old” pharmaceuticals should be devised and promptly implemented (SRU 2007). A research project to develop a concept for a monograph system for veterinary pharmaceuticals was sponsored by the German Federal Environment Agency UBA. This has led to the development of an approach for a systematic assessment of existing substances in veterinary pharmaceuticals products.

**Pharmaceuticals and water management**

In Europe no legally-binding quality threshold values exist for the occurrence of active pharmaceutical substances in surface waters and in groundwater.

The European Water Framework Directive (200/60/EC) (EC 2000) allows the definition of quality standards for pollutants. The directive aims at achieving a good ecological and chemical surface water status. Good status means, among other things, that concentrations of “priority substances” (relevant for all European member states) and “river-basin specific” synthetic and non-synthetic pollutants (relevant for special river basins or member states) do not exceed defined environmental quality standards for water, sediment and biota. When setting up management plans for river basin districts to achieve the aims of the Water Framework Directive, environmental quality standards for pharmaceuticals should be included.

In Germany recommendations exist on water quality standards based on ecotoxicological data for the anti-epileptic substance carbamazepine, the anti-inflammatory drug diclofenac and the blood lipid regulator clofibric acid. Results of monitoring show that the proposed quality standards are exceeded in surface waters for diclofenac and carbamazepine (see Table 1).
Table 1: German recommendations for water quality standards for active ingredients of human pharmaceuticals in the context of the Water Framework Directive and monitoring results (German Federal Environment Agency UBA, Working Group of the Federal States on Water Problems LAWA, unpublished data)

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Recommended Quality Standard (QS)</th>
<th>Monitoring Results</th>
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<tbody>
<tr>
<td>carbamazepine</td>
<td>0.5 μg/l</td>
<td>QS exceeded at &gt; 10% of all monitoring sites</td>
</tr>
<tr>
<td>diclofenac</td>
<td>0.1 μg/l</td>
<td>QS exceeded at &gt; 25% of all monitoring sites</td>
</tr>
<tr>
<td>clofibrac acid</td>
<td>5 μg/l</td>
<td>QS not exceeded</td>
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For drinking water the Drinking Water Directive 98/83/EC (EC 1998) sets a framework for European levels, but no threshold values for pharmaceuticals are currently defined. The German Drinking Water Commission recommends a precautionary threshold value of 0.1 μg/l for both human and veterinary drugs.

**Risk management beyond environmental assessment legislation**

Activities for reducing the exposure of the environment to pharmaceuticals have not only focused on environmental risk legislation. Risk management strategies for minimizing pollution of the environment with other contaminants, such as organic pollutants, heavy metals, pesticides and pathogens, often at the same time, leads to reduced exposure of the environment to drugs.

The upgrading of wastewater treatment technology in Europe, for example, contributes to a reduction of the concentration of pharmaceuticals in surface waters. The incineration of municipal solid waste instead of sending it to landfill sites prevents medicinal active substances from leaching into groundwater (Doerr-MacEwen, Haight 2006).
Further measures beyond authorization should focus on:

- technical measures
- changes in prescription routines and/or consumers’ decisions
- implementation of potential risks to the environment as a criterion in the development of pharmaceuticals
- legal restrictions for waste disposal and spreading of sewage sludge on agricultural lands.

Recently, a German research project START (sponsored by the German Federal Ministry of Education and Research) worked out options of action for reducing the contamination of water bodies with pharmaceuticals for human use (START 2008). A selection of options was identified, the implementation of which could contribute to a sustainable flow of pharmaceuticals (see Table 2).

A main project focus was the disposal of medicinal products. The best way of ensuring that pharmaceutical residues are properly disposed of in accordance with the substance risk is via a pharmacy-based collection system. This is because the pharmacist has the necessary technical expertise to assess the potential substance risk. Directive 2004/27/EC called on Member States to set up a suitable return system for medicine residues by the end of October 2005 (EC 2004a). In Germany, 15,000 out of a total of 21,000 public pharmacies are currently linked to the return system of the largest supplier (SRU 2007).

Today, only one third of Germans consistently return their unused or expired medicinal products to the pharmacy. In order to increase this number, a wide-range, professionally planned and organised campaign for educating the public is necessary. Supportively, an appropriate statement on the proper disposal of medicinal products should be printed by default on the medicinal product packing and on the package leaflet. A standard disposal advice should be “Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures are precautionary”. A threshold value will help to protect the environment and is incorporated into EU legislation but has so far not been consequently implemented. The pharmaceutical industry in this case is called on to go ahead pro-actively.
Table 2: Options of action for reducing the contamination of water bodies with pharmaceuticals for human use (START 2008)

<table>
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<tr>
<th><strong>Research Funding Programs for Green Pharmaceuticals</strong></th>
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<tr>
<td>This measure is intended to demonstrate the feasibility and economy of green active pharmaceuticals ingredients and to promote the implementation of the new molecular design principle in research and development. It should be accompanied by a gradual change in the university education of chemists, pharmacists and physicians…</td>
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<th><strong>Adjustment of University Education</strong></th>
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<tr>
<td>Chemists and pharmacists should be familiarised with the principles of sustainable chemistry and pharmacy and the methods of computer-assisted molecular design through the gradual adjustment of university curricula. Physicians should be instructed in their education particularly on the consequences of consumption and disposal of medicinal products for the environment…</td>
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<th><strong>Increasing Problem Awareness of Physicians and Pharmacists</strong></th>
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<tr>
<td>Discussion opportunities through publications in relevant media and supplementation of professional retraining enable physicians and pharmacists to form opinions on the topic of “Drinking water and water body contamination by active pharmaceuticals ingredients” and thus enhance their problem awareness. In this fashion, the basis is created for also realising directly effective options of action – such as the use of an environmental classification for human pharmaceuticals – in the professional routine…</td>
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<tr>
<th><strong>Introduction of an Environmental Classification for Human Pharmaceuticals</strong></th>
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<tr>
<td>An environmental classification for human pharmaceuticals should be introduced in Germany in a joint initiative by official bodies, manufactures of medicinal products, medical and pharmacy associations, and the research community, Here, imitation of the Swedish system is explicitly recommended…</td>
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<th><strong>Creation of an Uniform Disposal Standard for Medicinal Products</strong></th>
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<td>Disposal of medicinal products in Germany should be uniformly controlled via existing take-back system in pharmacies. To achieve this, the establishment of a binding disposal standard in the framework of the German Life-Cycle Resource Management Act is necessary…</td>
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<th><strong>Awareness Campaign on Proper Disposal</strong></th>
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<td>The population should be provided with information in widely applied awareness campaigns on the proper disposal of unused or expired medicinal products. The subject of water body pollution by active pharmaceutical ingredients should be emphasised in such a way that the correct disposal behaviour is conveyed as a positive experience without reinforcing possibly existing anxieties. In complement, medicinal product manufactures should consequently implement the existing EU regulations on placing corresponding disposal instructions on product packaging and in the package leaflet…</td>
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<th><strong>Special Enactment of Standards for Sustainable Sanitation Systems</strong></th>
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<td>Technical standards relating to the installation and operation of sustainable sanitation systems should be enacted, initially in selected sectors of building industry (new housing projects, commercial and industrial complexes, and hospitals)…</td>
</tr>
</tbody>
</table>
Summary

Current European legislation demands that the risks posed by pharmaceutical products are assessed before they enter the environment. Information required for this purpose focuses on fate and effects of pharmaceuticals in the environment. Since the guidelines for environmental risk assessment of human and veterinary pharmaceuticals came into force, dossier quality is improving and full risk assessment dataset submissions are increasing. This data will be used for a revision of the guidelines, a review of the action limits, suitability of tests and identification of substances with potential effects in the environment at low concentrations.

A sustainable approach also requires environmental risk assessment for existing substances. Based on similar programmes for existing chemicals or pesticides, a European programme for “old” pharmaceuticals should be devised and promptly implemented.

Active ingredients of pharmaceuticals should be included in the lists of priority and of river-basin specific substances of the Water Framework Directive. Quality standards for relevant substances then have to be defined. For drinking water, a precautionary threshold value should be set for medicinal active substances.

Risk mitigation management beyond environmental risk assessment legislation is important and necessary. Here a main focus should be on the disposal of medicinal products.
References


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The primary focus in his research is to study the eco-toxicological effects that for example single chemical substance, leachate water and sediments might have on aquatic organisms. In addition to this, he has a great interest in trying to improve environmental risk assessment by developing new strategies and methods. As a senior lector at Stockholm’s University, tutoring within different levels of knowledge is a fundamental part of his work with research. Project leader in the MistraPharma programme.

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B.sc and Honorary Doctorate. Previous vice CEO within the consultant company Sensia Konsulter, general manager in “Region Skåne” and county council manager in Jämtland. He is engaged in issues regarding society and different developing projects, especially within the field of health and healthcare.

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Environmental scientist. Pioneered the US EPA’s involvement with the many issues surrounding pharmaceuticals in the environment (PiE) beginning in the late 1990s. Created the world’s first web site devoted to PiE (in 2000) and made a series of contributions for advancing environmental stewardship and pollution prevention - “the green pharmacy”.

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Jerker Fick is a pharmacist and a researcher within environmental chemistry. He performs research about the destiny of pharmaceuticals in the environment and potential bioaccumulation in aquatic organisms. In addition to that, he is investigating different kind of environmental effects such as the development of antibiotic immunity.

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Jes la Cour Jansen has been a professor at Lund’s Institute of Technology since 1998. His research is primary about how to integrate new techniques at municipal wastewater treatment plants. The previous years he has been focusing on biological phosphorous separation, processes that reduce substances difficult to degrade as well as optimizing biogas production. Project leader in the MistraPharma programme.

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Physician focused on the linkages between the environment and human health. Pioneered research on leftover, unwanted medications, with emphasis on the causes, sources of their entry to the environment via disposal, new approaches for quantifying the magnitude of disposal, and ways to minimize or reduce the generation of leftover drugs.
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Researcher in the broad area of chemical and molecular pharmacology with specific reference to receptors and ion channels. Author and editor of multiple publications and books in these areas. Current focus on science policy and science ethics and director of Science and Public Program at the University of Buffalo.

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Research on the environmental behaviour of anthropogenic compounds, such as persistent organic pollutants and pharmaceuticals. His work includes e.g. studies of transport and fate processes and development of analytical techniques. The interactions between inherent physico-chemical properties and environmental matrices, including development of QSARs, are of special interest. Project leader in the MistraPharma programme.

Margot Wallström

Vice-President of the EU Commission, responsible for Communication Strategy and Institutional Relations.

She has been the EU Environment Commissioner and played a significant role in negotiating the Kyoto Protocol. For her, promoting sustainable development is also about promoting democracy and social justice, and thus should be a vital part of EU politics as well as on national level.
Åke Wennmalm  
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Physician and cardiovascular researcher. In collaboration with Bo Gunnarsson, Apoteket AB, initiated the Swedish work to lift the issue of pharmaceuticals in the environment in the EU, among pharmaceutical producers and in the health care system. Participated in the development of the environmental classification system for pharmaceuticals.

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