

A young child with long, wavy blonde hair is shown from the back, looking out over a vast, shimmering blue ocean under a clear sky. The child's hand is raised to their forehead, shielding their eyes from the sun. The overall mood is serene and hopeful.

# A Healthy Future

Pharmaceuticals in a Sustainable Society

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

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# **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.

A handwritten signature in black ink, appearing to read 'Ethel Forsberg'. The signature is fluid and cursive, with a large initial 'E' and a long, sweeping tail.

Ethel Forsberg

Director-General of the Swedish Chemicals Agency  
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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.





# 1

## **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](http://www.healthvault.com)) and Google Health ([www.google.com/health](http://www.google.com/health)), to those that are implemented by the healthcare industry, like the pioneering program of the Cleveland Clinic: MyChart ([elevelandclinic.com/cms/mychart.html](http://elevelandclinic.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](http://www.23andme.com)) and deCodeMe ([www.decodeme.com](http://www.decodeme.com)), followed by a service offered by Navigenics ([www.navigenics.com](http://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 physico-chemical 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 denaturing 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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