Reducing the Ecological Footprint of Pharmaceutical Usage:

Linkages between Healthcare Practices and the Environment

Christian G. Daughton, PhD
Chief, Environmental Chemistry Branch
National Exposure Research Laboratory
U.S. Environmental Protection Agency
944 East Harmon Avenue
Las Vegas, Nevada 89119

Ilene Sue Ruhoy, MD, PhD
Assistant Professor, Basic and Clinical Sciences
Touro University Nevada
College of Osteopathic Medicine
Henderson, NV 89014

Introduction

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

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

Without question, pharmaceuticals play extraordinarily important roles in the protection and improvement of human (and animal) health and well-being. Treatment (palliative, symptomatic and sometimes curative) and prevention of disease, together with improved quality of life, are highly visible aspects of a global industry with predicted sales in 2009 exceeding US$800(BN)

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

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

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

Behind the scenes of the extremely visible, prominent roles played by pharmaceuticals in healthcare is another world where pharmaceuticals are involved in a wide spectrum of other, largely hidden and unintended actions — potentially having unanticipated consequences for both human and ecological health. These invisible roles involve a wide array of pathways that lead to unintended (and perhaps unrecognized) exposure and serve to show the interconnectedness of the activities, actions, and behaviors of humans with the environment (Figure 1). In the final analysis, human health and ecological integrity are intimately linked. Actions designed to maintain, alter, or improve human health and well being have consequences for the environment, which in turn can feed back to impact human health — for example by way of recycling ambient environmental residues through drinking water (Daughton 2008).

Drug residues (from both human and veterinary usage) touch the environment in many ways. They can contaminate: surface and ground waters (via discharge or escape of treated and raw sewage and manure, and disposal of leftover drugs and medicated feeds); arable soils and crops (via use of recycled sewage for irrigation and biosolids for soil amendments); objects that we physically contact [via residues transferred from skin (Daughton and Ruhoy 2009)]; sediments

(via sorption); and biota (via bioconcentration) (Daughton and Brooks 2011 - in press). These pathways can all cycle back to human exposure via drinking water and foods (Daughton 2008, 2007).

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

The visible and hidden worlds of pharmaceuticals have never been treated together as integral parts of the lifecycle of drugs. A major reason 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. In return, a major unanticipated, collateral benefit could be the optimization of the delivery of healthcare in terms of both therapeutic outcomes and cost (Daughton and Ruhoy 2008). The various roles played by pharmaceuticals in healthcare are currently not in balance with the needs of the ecological environment, nor arguably with the needs of public health and well-being. For example, the WHO notes that proper management of healthcare waste (including disposal of expired pharmaceuticals) is a “public health imperative: that is part of the WHO’s core principles for achieving safe and sustainable management of health-care waste” (WHO 2007). Yet there is currently no international consensus - or consensus within the U.S. - regarding the disposal of unwanted medications.

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

Despite the thousands of publications over the last two decades on various aspects of pharmaceuticals as environmental pollutants (US EPA 2008b), it has only been recently proposed that actions to reduce the environmental impact of pharmaceuticals also can have reciprocal, collateral, positive outcomes for human health — for example, as a result of modified medical practices (e.g., more prudent and appropriate prescribing) and as a result of reduced exposure to environmental residues (Daughton and Ruhoy 2008). Indeed, possibly missing from green product design and development with respect to sustainable pharmacological care might be a formal evaluation of whether the actions designed to minimize environmental impact have

reciprocal benefits for the quality of human health (such as a lower incidence of adverse reactions and improved therapeutic outcomes).

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

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

Over the last century, the direction in which the practice of medicine has been headed holds tremendous promise not just for countless improvements in healthcare, but also for greatly reducing its environmental footprint. 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. The shift began to be formalized in the US in 1948 with establishment of the American Board of Preventive Medicine and Public Health (which shortened its name in 1952 to the American Board of Preventive Medicine - ABPM). Facilitating this is the emergence and convergence of personalized medicine and medical genetics/epigenetics, as well as advanced informatics and other information technology. This paradigm shift has been made possible primarily by advancement in understanding the human genome (and biomarkers based on the many other “omics” subdisciplines, such as proteomics, metabolomics, and glycomics) and by advancements in analytical chemistry, computer technology, and bioinformatics, required to handle the voluminous, complex, rich array of data generated by the omics fields.

Improving the Efficiency of Pharmacy

Mining of Healthcare Data

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

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

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

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

While these deficiencies persist, could existing data in the interim be used to answer some key questions, such as the degree to which a medication is fully consumed or left over? Some of the

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

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

Electronic Systems

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

The early stages of digital solutions targeted for the consumer range from those that are publically accessible, such as Microsoft's HealthVault (http://www.healthvault.com/) and Google Health (www.google.com/health) to those implemented by the healthcare industry, such as the pioneering program of the Cleveland Clinic: *MyChart* (http://eclevelandclinic.com/cms/mychart.html), and e-prescribing as facilitated under the Nationwide Health Information Network (NHIN) (see discussion below); systems that aggregate data across disparate systems [such as *Amalga* (Microsoft 2009)] are key to providing healthcare professionals with a unified, common view of patient histories and needs. After all, most patient medical information is currently not digitized and therefore provides limited value to physicians, pharmacists, or patients themselves.

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

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

Personalized Medicine - a Framework for a Sustainable Pharmacy

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

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

In the early 1990s, PM referred to the rather general and vague notion of a patient-centered practice of medicine. The idea developed momentum in the late 1990s with the advancement of the Human Genome Project (Adam et al. 1999). It has since developed more concrete, specialized embodiments. The journal *Personalized Medicine* was launched just in 2004. The

Personalized Medicine Coalition (PMC) was founded in 2003 (http://www.personalizedmedicinecoalition.org), and the Partnership for Personalized Medicine was formed in 2007. Several terms have evolved to describe various dimensions of PM, including: pharmacogenomics (PGx), targeted medicine, predictive medicine, smart medicine, rational drug therapy (Ekedahl 2002), precision medicine, evidence-based medicine, outcomes-based medicine (vs. symptom-based), tailor-made medicine, stratified medicine (Trusheim et al. 2007), and customized care. 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/dispensing errors (SACGHS May 2008). This empirical approach to prescribing, with its many limitations, has led to the advent in Europe of pay-for-performance pricing (cost-justified payment systems) for pharmaceutical treatment (Pollack 2007).

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

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

Even the drugs used most widely — the "blockbuster drugs" — typically show efficacy in only 40-60% of patients (PricewaterhouseCoopers 2005). In a well-publicized remark, Allen Roses, a vice-president of GlaxoSmithKline, stated that "the vast majority of drugs — more than 90 per cent — only work in 30 or 50 per cent of the people" (Anonymous 2005).

This means that for roughly the majority of usage, drugs are being used inefficiently at best or inappropriately or imprudently at worst. Such non-targeted usage, in turn, can promote the need for auxiliary medications to counteract side effects as well as additional medications to further assist in treatment of the original symptoms. If the majority of drug usage is unwarranted, this

leads to gross over-usage and accumulation of leftover drugs from non-compliant patients, who often comprise the poor-responders and non-responders. This excessive use then results in the unwarranted introduction of APIs to the environment, from sources that could have been avoided — excretion, bathing, and disposal.

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

Pharmacogenomics (PGx)

A prime objective of personalized medicine is to take into account the many differences between individuals and how these variables interact. Differences include genetics (such as slow and fast metabolizers and non-responders), 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. Screening tests designed to identify these sub-groups that do not respond properly to a drug can be used to "rescue" a drug from failure during clinical trials and to attain regulatory approval. In addition, those with particular polymorphisms of disease can be treated with different regimens than others with a similar diagnosis (e.g., hormone-responsive cancers). The important role played by chronobiology (Smolensky and Peppas 2007) with regard to the timing of drug delivery is exemplary of the many factors that have yet to be widely implemented in personalized medicine. The delivery of a medication timed according to natural rhythms not only can lessen the incidence of adverse reactions, as with chemotherapy, but in some instances it also allows for lower (or higher but less frequent) doses. Timing of a dose can affect both pharmacokinetics and pharmacodynamics. As personalized medicine develops, more specialized segments of pharmacotherapy, such as chronotherapeutics, will emerge as common modes of therapy.

For a truly sustainable pharmaceutical treatment model, considerations for environmental impact would need to be incorporated — to minimize excretion of bioactive parent APIs or metabolites

(including conjugates subject to reversible metabolism back to the parent aglycone) and minimize leftover medications that would otherwise require disposal. Probably the first formalized program to begin taking some of these many factors into consideration was the environmental classification system introduced in 2003 and further refined by the Stockholm County Council (2008).

Inefficiencies in medical prescribing and in dispensing often translate directly into added impacts on the environment. The costs of suboptimal drug therapy primarily revolve around drug-induced morbidity and mortality and poor response to treatment. By reducing the incidence of sub-optimal therapy, not only would health outcomes vastly improve and patient expense diminish, but drug use in many cases could be reduced, thereby leading to lower potential for impact on the environment.

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

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

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

In the U.S., the number of NMEs withdrawn from the market for safety reasons over the last 3 decades has totaled about two dozen, and represented roughly 3% of the total NMEs approved

(Anonymous 2008; Kaitin 2005). With tests that could reveal the stratified populations for which these NMEs (and those with box warnings) would result in adverse reactions, these NMEs could possibly be reintroduced or used with vastly improved safety with relabeling.

Development of test procedures (known as diagnostic-therapeutic tandems, companion diagnostics, "theranostics," or pharmacodiagnostics) to target the appropriate sub-populations could greatly increase the approval rate for drugs while vastly improving their efficacy (in the target population). The potential for increasing the apparent effectiveness of a drug could theoretically approach 100%. The integration of pharmacogenomics with companion diagnostics to accurately target the selection of optimal drugs and their dosages, and the optimal duration of therapy, results in what are known as drug/test combination products (Warner 2004); the first combination product, approved in 1998 by the FDA (HercepTest/Herceptin), was for HER2-positive breast cancer; the diagnosis of HER2-positive breast cancer itself is a result of medical genetic testing. Pharmacogenomic information (specifically genomic biomarkers) useful in selecting appropriate medications for individual patients is increasingly being included with approved drugs; see the list maintained by the US FDA (US FDA 2008a) .

Outlook for Personalized Medicine – extending the focus from treating symptoms to achieving efficacious therapeutic outcomes

The advent of mainstream PM and its many innovations will pose major challenges for a wide range of stakeholders, all of whom will need to begin working closely to coordinate their efforts. Ethical and public concerns will demand careful attention — not just secured protection of personal information by healthcare professionals, clinical researchers, and the health insurance industry, but also selection or exclusion of participants for clinical trials and appropriate 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 (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). Some of the quandaries posed by genetic testing are discussed by Korobkin and Rajkumar (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. Of equal importance is that the tests need to have clinical utility — the results need to potentiate outcome-oriented actions on the part of the physician and patient. Over 1,500 medical conditions can now be revealed by genetic testing. While their current usefulness or efficacy is open to debate, personal genetic testing became readily available directly to the consumer in 2007 —

tests primarily using DNA chips that can reveal thousands of SNPs; the first available were *23andme* (https://www.23andme.com/) and *deCodeMe* (http://www.decodeme.com/), followed by a service offered by Navigenics (http://www.navigenics.com/).

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

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

Clearly, personalized medicine has great potential for altering the usage of pharmaceuticals, in terms of both the quantities and types of APIs. PM therefore has the potential for indirectly and passively reducing environmental impacts of APIs by simply reducing their initial entry to the environment. More direct and active intervention in reducing environmental impact can be taken by addressing the many factors that dictate the environmental footprint of an API, beginning with the drug development process itself. Drug development is driven not just by measures of efficacy and safety, but also by factors unrelated to patient use or benefit, such as drug and target discovery, drug design and formulation, synthesis, production, manufacture, packaging, and marketing. The long and complex decision process required for determining whether to proceed with commercializing a drug could be augmented with the factors that dictate environmental impact, including persistence and potential for bioconcentration (e.g., Gunnarsson and Wennmalm 2008; Stockholm City Council 2008) as well as pharmacokinetics contributing to extensive excretion (or conjugation) or pharmacodynamics involving receptors in non-target

species. Candidate APIs that have undergone and passed screening for environmental impact may also have a higher probability of passing clinical trials, simply because they may necessarily have a lower incidence of adverse effects.

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

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

Improving Drug Delivery & Chemistry by Design

In the U.S., the Pollution Prevention Act of 1990 encouraged the U.S. 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 APIs and in striving to make drug-based medical care more sustainable. Opportunities for the application of green chemistry span the spectrum from drug design, formulation, delivery, and packaging, to waste treatment. Progress in any of the following, for example, serves to reduce the footprint of APIs: (i) streamlining drug discovery [e.g., capitalizing on ethnobiology, which in turn can catalyze the protection of endangered geographic locales (e.g., Mihelcic et al. 2007)], (ii) synthetic routes that rely less on hazardous reactants, reduce production of hazardous waste, or lower energy consumption, such as use of biocatalysis (Woodley 2008), (iii) optically pure APIs (eliminates non-therapeutic isomers and reduces overall dose) (Daughton 2003), (iv) chemical

structures more amenable to microbial and chemical structural transformation or degradation, which lead to shorter environmental half lives and reduced potential for bioconcentration in non-target organisms (Daughton and Brooks 2011 - in press), and structural transformation to more innocuous end products, (v) structures, formulations, or delivery devices that facilitate the API to selectively reach its biological target (thereby reducing dosage), (vi) packaging that promotes longer shelf life or provides accurate real-time indication of expiry status (e.g., Galagan and Su 2008), reducing the need for disposal [especially important for those drugs sensitive to light, moisture, or oxygen (e.g., Rosenberg et al. 2008)], and (vii) destructive waste treatment approaches that can be adopted by existing waste and drinking water treatment facilities or even by healthcare/consumers.

Drug packaging alone can play a large role in leading to the need to dispose of drugs. Possible improvements include reinventing to enhance security (e.g., ensuring tamper proofing is one limitation to drug recycling), providing visual confirmation of whether a medication has reached expiry prematurely (e.g., because of storage in excessive heat or humidity) or if it has not truly become unusable by the label date, and developing easy means of testing actual shelf life [some drugs can have shelf lives that far exceed the default 1 year (e.g., see: Daughton 2003)]. These improvements might greatly facilitate the safe reuse of previously dispensed medications or the sustained use of medications erroneously thought to have expired. The composition and physical design of packaging itself could also be optimized to reduce its own environmental footprint (especially reducing resources required for manufacture and wastes created during disposal).

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

On the down side with respect to potential environmental impact, improved delivery could facilitate the increased use of ultrapotent APIs, which could counterbalance any environmental gains from reduced dose. While an ultrapotent API would reduce its overall mass loading in the

environment (from excretion or bathing), the greatly increased potency of the API may serve to re-adjust the potential for its effects in the environment. Another example is a new class of radiopaque iodinated polymers that are biodegradable, as opposed to those iodinated X-ray contrast agents that are currently widely used and quite persistent (Carbone et al. 2008).

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

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

“Pharmaceutical Care”: an Avenue to Improved Health Care and Reduced Environnemental Footprint

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

publications over the last few decades; some of the more recent examples include: Berenguer et al. (2004), Martin-Calero et al. (2004), Pearson (2007), and van Mil et al. (2004).

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

Healthcare will probably see a continued evolution toward closer working relationships between pharmacists and physicians. Many different models of practice will undoubtedly emerge, involving an array of physician/pharmacist collaborations or partnerships, where pharmacists could eventually become pharmacotherapy experts working as integral parts of medical practices (see: White and Latif 2006). Indeed, hospital care teams usually consist of a pharmacist with the sole purpose of consultation on treatment implementation and monitoring of hospitalized patients. The traditional role of dispensing could transition away from pharmacists, toward pharmacy technicians, using increasingly more sophisticated automation and computerized knowledge systems. Dispensing could be more tightly regulated with respect to quality control, one obvious outcome being to greatly minimize dispensing errors (and thereby help to reduce the incidence of unused drugs). By linking such systems with real-time databases for ADRs and with information needed for personalized medicine, the possibility 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 one of many examples.

Portions of such an electronic framework are emerging in the U.S. in the form of e-prescribing, as facilitated by the Nationwide Health Information Network (NHIN) under the U.S. Department of Health & Human Services (HHS 2009) and as the e-prescribing network operated by Surescripts (Surescripts 2009); as a pioneering venture in e-prescribing, Surescripts is the largest commercial, real-time, nationwide prescribing and information exchange network, which in part provides a patient’s medication history and decision support tools for physicians. In-depth perspectives on electronic connectivity in healthcare are provided by the eHealth Initiative (2008) and the Markle Foundation (2008). In the 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); this legislation, however, was not adopted into law. All of these advancements will undoubtedly lead to a reduction in unwarranted or mistaken prescribing and dispensing (as well as improved patient compliance), with the obvious benefits accruing to human health and the economy as well as ecological impact. Of course, e-prescribing

could also serve to increase the use of certain medications, as it is known, for example, that e-prescribing can increase compliance with filling prescriptions.

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

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

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

Extrinsic forces that will act as forcing functions could be dominated by climate change and the changing age structure of society. Climate change could dramatically influence the use of pharmaceuticals, as dictated by emerging or exacerbated problems surrounding cardiopulmonary and infectious diseases (e.g., vector and water-borne), allergy, and physiological stresses (e.g., heatstroke), each having strong associations with the young and elderly (e.g., see: Ebi et al. 2006; Patz et al. 2005).

By analogy with the concepts of the "ecological footprint" (which quantifies the land area needed to sustain per capita living) and the derived concept of the "water footprint" — the water required to sustain a population (e.g., Hoekstra and Chapagain 2007) — perhaps the central question needing examination with respect to the sustainability of medication usage and the

intersection between human and ecological health is "What types and quantities of medications are needed to optimize the health and well-being of society, balanced against the integrity of the environment?" Can the prescribing and consumption of medication serve as an overall measure of societal and ecological health and well-being? A virtual healthcare system — one working perfectly — would generate no leftover medications. In a perfect, sustainable system, all humans and domestic animals would receive exactly the type, degree, and duration of treatment required for optimal and cost-effective therapeutic (and lifestyle) outcomes, and any excreted residues of parent API or bioactive metabolites could be degraded in the environment with minimal adverse impact. Leftover drugs are diagnostic of any number of deficiencies in the chain of systems spanning from the design of drugs and packaging, advertising, prescribing, and dispensing, to ultimate patient use. Reducing the footprint of medication holds considerable potential for benefiting both human health and the environment.

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

REFERENCES

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

Anonymous (2005) Medicine Gets Personalised. Chemistry World (Royal Society of Chemistry) July, available: http://www.rsc.org/chemistryworld/Issues/2005/July/Medicine_personalised.asp

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

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

Bajcar JM, Kennie N, Einarson TR (2005) Collaborative medication management in a team-based primary care practice: An explanatory conceptual framework. Research in Social and Administrative Pharmacy 1:408-429

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

Berenguer B, La Casa C, de la Matta MJ, Martin-Calero MJ (2004) Pharmaceutical Care: Past, Present and Future. Current Pharmaceutical Design 10:3931-3946

Bernini P, Bertini I, Luchinat C, Nepi S, Saccenti E, Schäfer H, Schütz B, Spraul M, Tenori L (2009) Individual Human Phenotypes in Metabolic Space and Time. Journal of Proteome Research (in press)

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

Carbone AL, Song M, Uhrich KE (2008) Iodinated Salicylate-Based Poly(anhydride-esters) as Radiopaque Biomaterials. Biomacromolecules 9:1604-1612

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

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

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

Crimmins WF (2001) Disposing of Expired Drugs: a Matter of Policy. J Am Vet Med Assoc 218:10

Daemmrich A, Bowden ME (2005) Emergence of Pharmaceutical Science and Industry: 1870-1930. Chem Eng News 83:(http://pubs.acs.org/cen/coverstory/83/8325/8325emergence.html)

Daughton CG (2002) Environmental stewardship and drugs as pollutants. The Lancet 360:1035-1036
Daughton CG (2003) Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ Health Perspect 111:757-774
Daughton CG (2004) PPCPs in the environment: Future research - beginning with the end always in mind. In: Pharmaceuticals in the environment: Sources, fate, effects and risks. Kümmerer K (ed). Springer, Berlin, Germany, 2nd edn
Daughton CG (2007) Pharmaceuticals in the environment: sources and their management. In: Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle. Petrovic M, Barcelo D (eds). Elsevier Science
Daughton CG (2008) Pharmaceuticals as environmental pollutants: the ramifications for human exposure. In: International Encyclopedia of Public Health. Heggenhougen K, Quah S (eds). Academic Press, Oxford, England
Daughton CG, Brooks BW (2011 - in press) Pharmaceutical Active Ingredients in Aquatic Organisms. In: Environmental Contaminants in Biota: Interpreting Tissue Concentrations. Beyer W, Meador J (eds). Taylor and Francis, Boca Raton, FL, 2nd edn
Daughton CG, Ruhoy IS (2008) The Afterlife of Drugs and the Role of PharmEcovigilance. Drug Safety 31:1069-1082
Daughton CG, Ruhoy IS (2009) Environmental Footprint of Pharmaceuticals - The Significance of Factors Beyond Direct Excretion to Sewers. Environmental Toxicology and Chemistry (in press)
Ebi KL, Kovats RS, Menne B (2006) An approach for assessing human health vulnerability and public health interventions to adapt to climate change. Environ Health Perspect 114:1930-1934
Eckerman I, Martineus J-C (1997) Medicines and the environment - what do we know today? , Swedish Association of Physicians for the Environment, Gray M. Stockholm, Sweden. http://www.dnsy.se/_upload/lfm/medicines%20and%20the%20environment.pdf
eHealth Initiative (2008) eHealth Initiative. eHealth Initiative, Foundation for eHealth Initiative. Washington, DC. http://www.ehealthinitiative.org/
Ekedahl A (2002) Statistics on local drug sales: A tool to identify problem areas and to follow effects of education on drug use. Doctoral dissertation, Department of Community Medicine, Malmö University Hospital, Lund University, Lund, Sweden, 54 pp
Fichana D (2005) Green Engineering and Gate-to-gate Life Cycle Assessments for Pharmaceutical Products. Masters dissertation, Rowan University, 142 pp
Galagan Y, Su WF (2008) Fadable ink for time-temperature control of food freshness: Novel new time-temperature indicator. Food Research International 41:653-657
Giacomini KM, Krauss RM, Roden DM, Eichelbaum M, Hayden MR, Nakamura Y (2007) When good drugs go bad. Nature 446:975-977
Gorard DA (2006) Escalating polypharmacy. QJM 99:797-800
Gunnarsson B, Wennmalm A (2008) Drug Design Should Involve Consideration of Environmental Risk and Hazard. Letters in Drug Design & Discovery 5:232-235
HapMap (2008) International HapMap Project. The International HapMap Consortium. http://www.hapmap.org/

Haskell SRR, Ormond CJ, Occhipinti LP, Powers EL (2003) Waste management: expired drugs. J Am Vet Med Assoc 223:51-52
Henderson RK, Jimenez-Gonzalez C, Preston C, Constable DJC, Woodley JM (2008) EHS & LCA assessment for 7-ACA synthesis. A case study for comparing biocatalytic & chemical synthesis. Industrial Biotechnology 4:180-192
Hepler C, Strand L (1990) Opportunities and responsibilities in pharmaceutical care. Am J Health Syst Pharm 47:533-543
HHS (2009) Nationwide Health Information Network (NHIN). U.S. Department of Health & Human Services. Washington, DC. http://healthit.hhs.gov/portal/server.pt?open=512&mode=2&cached=true&objID=1142
Hoekstra AY, Chapagain AK (2007) Water footprints of nations: Water use by people as a function of their consumption pattern. Water Resour Manage 21:35-48
Hudson KL, Holohan MK, Collins FS (2008) Keeping Pace with the Times -- The Genetic Information Nondiscrimination Act of 2008. N Engl J Med 358:2661-2663
IMS (2008) IMS Health Forecasts 4.5 – 5.5 Percent Growth for Global Pharmaceutical Market in 2009, Exceeding $820 Billion. IMS Health Incorporated. http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=9e553599b554d110VgnVCM100000ed152ca2RCRD&vgnextfmt=default
Joly BM, Polyak G, Davis MV, Brewster J, Tremain B, Raevsky C, Beitsch LM (2007) Linking accreditation and public health outcomes: a logic model approach. J Public Health Manag Pract 13:349-356
Kaitin KI, (ed.) (2005) Drug safety withdrawals in the U.S. not linked to speed of FDA approval. Tufts CSDD (Center for the Study of Drug Development) Impact Report 7:1-4
Katsanis SH, Javitt G, Hudson K (2008) A Case Study of Personalized Medicine. Science 320:53-54
Khetan SK, Collins TJ (2007) Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry. Chem Rev 107:2319-2364
Korobkin R, Rajkumar R (2008) The Genetic Information Nondiscrimination Act -- A Half-Step toward Risk Sharing. N Engl J Med 359:335-337
Krutzfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, Stoffel M (2005) Silencing of microRNAs in vivo with 'antagomirs'. Nature 438:685-689
Kuehn BM (2008) Traces of drugs found in drinking water: Health effects unknown, safer disposal urged. J Am Med Assoc 299:2011-2013
Kummerer K (2007) Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry. Green Chem 9: 899-907
Kummerer K, Velo G (2006) Ecopharmacology: A New Topic of Importance in Pharmacovigilance. Drug Safety 29:371-373
Kuspis DA, Krenzelok EP (1996) What happens to expired medications? A survey of community medication disposal. Vet Hum Toxicol 38:48-49
Levy W (2008) Peptide Progress: Refined manufacturing and delivery promises more advanced drug offerings. Pharmaceutical Formulation & Quality 10:28-30,32
Markle Foundation (2008) Connecting for Health. The Markle Foundation. http://www.connectingforhealth.org/

Martin-Calero MJ, Machuca M, Murillo MD, Cansino J, Gastelurrutia MA, Faus MJ (2004) Structural Process and Implementation Programs of Pharmaceutical Care in Different Countries. Current Pharmaceutical Design 10:3969-3985

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

Mihelcic JR, Zimmerman JB, Ramaswami A (2007) Integrating Developed and Developing World Knowledge into Global Discussions and Strategies for Sustainability. 1. Science and Technology. Environ Sci Technol 41:3415-3421

Moynihan R (2008) Key opinion leaders: independent experts or drug representatives in disguise? British Medical Journal 336:1402-1403

NIH (2008) NIH Roadmap Initiatives. Office of Portfolio Analysis and Strategic Initiatives, National Institutes of Health Bethesda, Maryland. http://nihroadmap.nih.gov/initiativeslist.asp

Patz JA, Campbell-Lendrum D, Holloway T, Foley JA (2005) Impact of regional climate change on human health. Nature 438:310-317

Pearson GJ (2007) Evolution in the practice of pharmacy--not a revolution! CMAJ 176:1295-1296

Phillips DP, Barker GEC, Eguchi MM (2008) A Steep Increase in Domestic Fatal Medication Errors With Use of Alcohol and/or Street Drugs. Arch Intern Med 168:1561-1566

Pinheiro C (2008) Drug donations: what lies beneath. Bulletin of The World Health Organization 86:580-581

Pollack A (2007) Pricing Pills by the Results. In: New York Times. New York Times

PricewaterhouseCoopers (2005) Personalized medicine: the emerging pharmacogenomics revolution. PricewaterhouseCoopers GTC, Health Research Institute. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf

Rahman SZ, Khan RA (2006) Environmental pharmacology: a new discipline. Indian J Pharmacol 38:229-230

Rosenberg J, Schilit S, Nathan J (2008) Which oral solid medications should be protected from light and/or moisture? In: Drug Topics, Drug Topics. http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252008/524496/article.pdf

Ruhoy IS, Daughton CG (2008) Beyond the medicine cabinet: An analysis of where and why medications accumulate. Environment International 34:1157-1169

SACGHS (May 2008) Realizing the Potential of Pharmacogenomics: Opportunities and Challenges. Secretary's Advisory Committee on Genetics, Health, and Society, chartered by U.S. Department of Health & Human Services. http://www4.od.nih.gov/oba/sacghs/reports/SACGHS_PGx_Report.pdf

Smolensky MH, Peppas NA (2007) Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Deliv Rev 59:828-851

Stockholm City Council (2008) Environmentally Classified Pharmaceuticals. http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=10205; via www.janusinfo.se/environment

Stoughton M, Votta T (2003) Implementing service-based chemical procurement: lessons and results. Journal of Cleaner Production 11:839-849

Surescripts (2009) 2008 National Progress Report on E-Prescribing. Alexandria, VA: Surescripts LLC. http://www.surescripts.com/downloads/NPR/national-progress-report.pdf
Thayer AM (2008) Filling A Highly Potent Niche: Drug companies want to create conjugates of potent drugs and biological molecules, and custom manufacturers are complying. Chemical and Engineering News 86:28-32
Tinetti ME (2008) Over-the-Counter Sales of Statins and Other Drugs for Asymptomatic Conditions. N Engl J Med 358:2728-2732
Trusheim MR, Berndt ER, Douglas FL (2007) Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov 6:287-293
Tucker JL (2006) Green Chemistry, a Pharmaceutical Perspective. Org Process Res Dev 10:315-319
Tudor TL (2007) Towards the development of a standardised measurement unit for healthcare waste generation. Resources, Conservation and Recycling 50:319-333
US Congress (24 June 2008) H.R. 6357: PRO(TECH)T Act of 2008 ("Protecting Records, Optimizing Treatment and Easing Communication through Healthcare Technology Act of 2008") 110th Congress, 2D Session, Washington, DC
US EPA (2008a) Green Chemistry Program at EPA. U.S. Environmental Protection Agency. http://www.epa.gov/gcc/pubs/epa_gc.html
US EPA (2008b) Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature. US Environmental Protection Agency. http://www.epa.gov/ppcp/lit.html
US FDA (2008a) Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Rockville, MD. http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm
US FDA (2008b) FDA's Sentinel Initiative: National Strategy for Monitoring Medical Product Safety. US Food and Drug Administration. http://www.fda.gov/oc/initiatives/advance/sentinel/
van Mil JWF, Schulz M, Tromp TFJD (2004) Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review. Pharmacy World & Science 26:303-311
Warner S (2004) Diagnostics + Therapy = Theranostics. The Scientist 18:38
White EV, Latif DA (2006) Office-Based Pharmacy Practice: Past, Present, and Future. Ann Pharmacother 40:1409-1414
WHO (1999) Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies. World Health Organization. http://www.who.int/water_sanitation_health/medicalwaste/pharmaceuticals/en/index.html
WHO (2007) WHO core principles for achieving safe and sustainable management of health-care waste. World Health Organization DfPHaE, Assessing and Managing Environmental Risks to Health, WHO/SDE/WSH/07.10. http://www.who.int/water_sanitation_health/medicalwaste/hcwprinciples.pdf; http://www.who.int/water_sanitation_health/medicalwaste/hcwprinciples/en/index.html
WHO (2008a) About the ATC/DDD system. The WHO Collaborating Centre for Drug Statistics Methodology Oslo. http://www.whocc.no/atcddd/atcsystem.html

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

Woodend K (2003) Medication management: The future of pharmaceutical care? Canadian Pharmaceutical Journal (CPJ) 136:29-31,46

Woodley JM (2008) New opportunities for biocatalysis: making pharmaceutical processes greener. Trends in Biotechnology 26:321-327

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

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

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

Figure 1. Environmental Lifecycle of APIs and Human Exposure. Points and factors in lifecycle that can be modified to reduce the environmental footprint of APIs.