Drugs and the Environment: Stewardship & Sustainability

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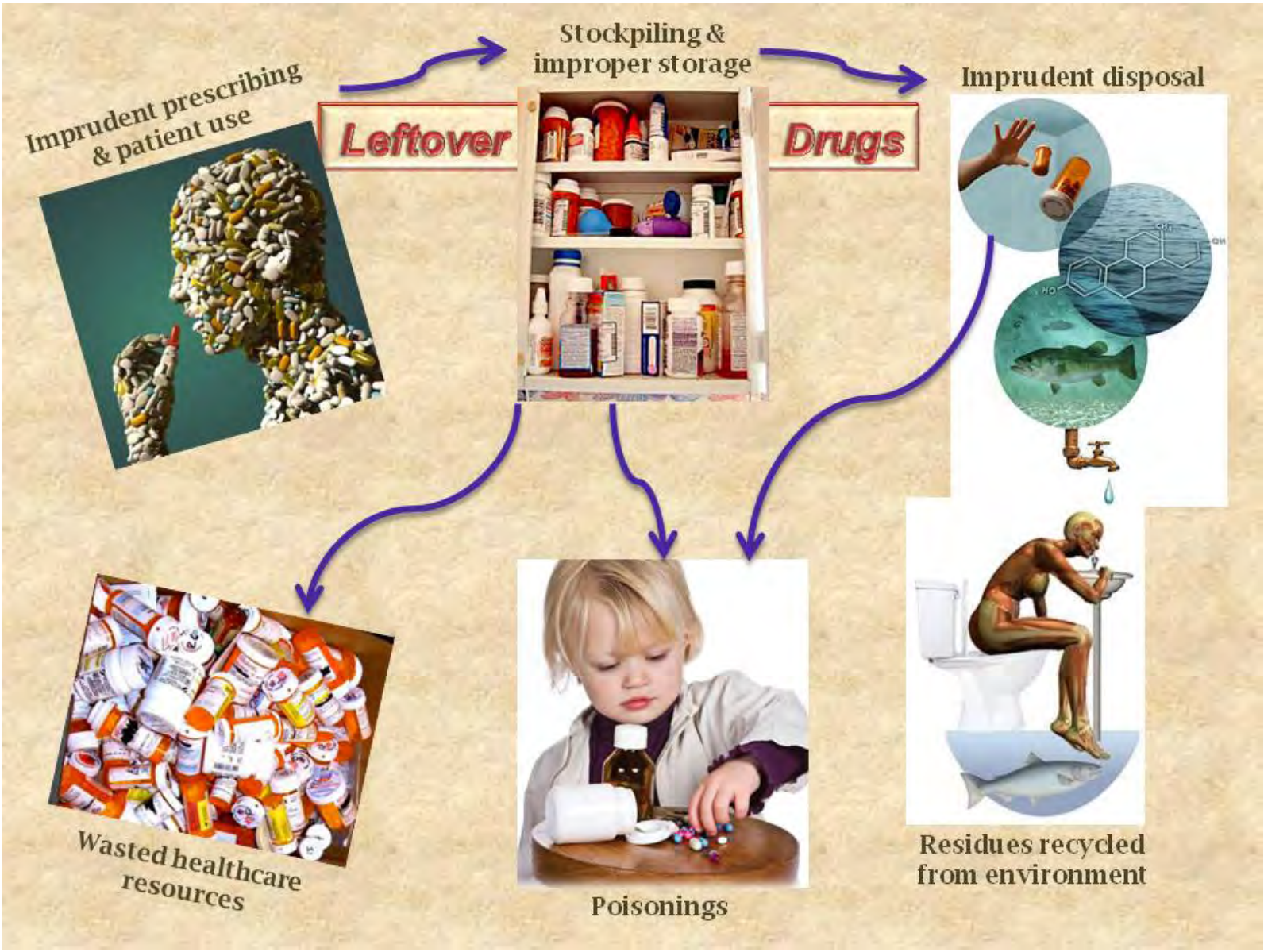
Imprudent prescribing & patient use
Stockpiling & improper storage
Imprudent disposal
Leftover
Drugs
Wasted healthcare resources
Poisonings
Residues recycled from environment

TABLE OF CONTENTS

Table of Contents 3
ABSTRACT 7
INTRODUCTION 8
Terminology and What Exactly Is Drug Wastage? 14
MAJOR FINDINGS and INSIGHTS 15
Overview 16
(1) The need for prudent drug disposal is not a new issue 16
(2) Drug disposal is a deceptively complex issue and one refractory to simple solutions 16
CAUSES of LEFTOVER MEDICATIONS 16
(3) The causes of accumulation of leftover drugs are numerous, complex, and not amenable to simple solutions 16
(4) A comprehensive approach for reducing the incidence of leftovers will require a full and accurate understanding of the entire cradle-to-grave life cycles of medications 17
DISPOSAL: SCIENCE ISSUES & CONCERNS 17
(5) Evidence for drug disposal acting as a major origin of ambient aquatic residues of APIs does not exist, except for some select cases 17
(6) Drug disposal may serve as the major source of APIs in landfills (even when not receiving biosolids) 18
(7) Disposal to trash poses unknowns with regard to the environmental fate of APIs 19
(8) Disposal to trash poses additional hazards 19
(9) Concerns regarding individual privacy during disposal can increase the risks for poisoning or injury 19
UNDER-RECOGNIZED CONCERNS or DRUG-USE PRACTICES 19
(10) Graywater and septic systems are under-recognized potential problems with regard to drug disposal 19
(11) Disposal of certain select delivery devices to sewers may serve as a major source of particular API residues in the environment 20
(12) Pharmacokinetics, dosage form, and patient compliance are the main factors dictating whether disposal can be a significant contributor to ambient environmental levels of APIs 20
(13) Certain drug-use practices can essentially serve as indirect, unintended, hidden forms of disposal 20
(14) Biologics pose little concern with regard to disposal to sewers, but do pose some concern with regard to disposal to trash 21
(15) Drug donations are a major problem for humanitarian relief efforts 21
DISPOSAL GUIDANCE 22
(16) Guidelines for prudent disposal need to avoid a singular focus on protecting the environment 22
(17) Current drug disposal guidance may be flawed and increase risks for humans 22
(18) Drugs possessing the potential for single-dose lethality require special consideration in disposal guidance 23
(19) Protecting the environment with optimal disposal guidelines can conflict with ensuring human safety 23

(20) Prudent drug disposal requires balancing the protection of the environment with ensuring access to timely medical care 24
FORMAL COLLECTION PROGRAMS 24
(21) The potential effectiveness of drug-collection programs for curbing imprudent disposal is unknown 24
(22) Formal collection programs for unwanted drugs may have significant hidden costs 24
(23) The statistical representativeness of data from drug collection or take-back programs is unknown 24
(24) Data from drug collection programs cannot be inter-compared; standardization is needed 25
(25) Prudent drug disposal requires attention not just to the API, but also to the packaging 27
(26) Drug collection programs (e.g., take-backs) may not be an effective approach for reducing the diversion of the primary drugs of concern - controlled substances 27
(27) Patchwork of take-backs in the US adds to the existing confusion regarding drug disposal 27
(28) Sustainable approaches to drug disposal require clear and useful measures of success 28
DRIVERS for ASSESSING MEDICATION WASTE 28
(29) Connection to Healthcare: Viewing leftover drugs as measures of success or opportunities for improvement, rather than simply as waste 28
(30) Focus on Source Reduction: An overwrought focus on drug disposal may distract from a sustainable solution yielding a wide range of collateral benefits 29
(31) Adopting Healthier Lifestyles: Reducing the incidence of leftover drugs may in some instances also serve to reduce the entry of APIs to sewers via excretion and bathing 30
(32) Counter to current perception, excretion of APIs can be reduced – without jeopardizing the quality of healthcare 30
(33) Several trends hold potential for exacerbating the need for prudent drug disposal 30
(34) Manufacturer promotions such as Direct-to-Consumer (DTC) advertising and drug sampling increase the incidence of leftovers 32
(35) Certain trends such as large-scale drug diversion may be exacerbating the need for drug disposal 33
MESSAGING & COMMUNICATION 33
(36) Current science can only justify a focus on drug disposal on the basis of the collateral benefits for healthcare and protecting human safety - not for protecting the environment 33
(37) Possible unexpected paradox: Drug take-back events may potentially worsen the drug disposal problem, as well as diversion and poisonings, by encouraging stockpiling 34
(38) Public outreach efforts designed to promote prudent disposal should try to ensure that certain, select groups are reached 35
(39) Public outreach efforts and mechanisms for prudent drug disposal should try to accommodate consumers with unusual needs 35
(40) Unknowns surrounding the connection of expired drugs with toxicity 36
(41) Non-compliance can be targeted as a means to better involve the patient in effecting change 36
(42) Centralized coordination needed for all issues related to stewardship and disposal - minimizing waste of resources that leads to duplication of effort, rediscovery, and reinvention 36
SCOPE AND OBJECTIVES 37
PROJECT COMPONENTS 41
HISTORICAL PERSPECTIVE 47

BACKGROUND AND RATIONALE 51
Overviews of the Drug Disposal Issue 56
Specific Areas of Research Relevant to Understanding the Origins of Leftover Drugs, the Significance of Drug Disposal, and the Importance of Stewardship 57
Non-compliance/Non-adherence 57
Introduction 57
The "healthy-adherer" or "healthy-user" effect. 60
Some of the many causes of (and means of controlling) non-compliance. 62
Shared decision-making and "brown-bag medication review." 65
Dispensed quantities - the roles of stat and PRN 66
Asynchronous repeat prescribing (misalignment) and inequivalence. 69
Role of the prescriber and rational prescribing. 70
Costs of non-compliance (and hospital wastage). 72
Technology, personalized medicine, and other approaches for improving compliance. 73
Leftover drugs as contributors to human poisonings 75
Data from poison control centers and coroner reports 78
Factors that can exacerbate poisonings - the roles of packaging (especially child-resistant closures - CRCs), drug design, and consumer behavior 79
Child-resistant closures (CRCs). 81
Single-dose lethality and fatal medication errors (FMEs) at home. 82
Transdermal and topical drug delivery systems (TDDS). 83
Leftover drugs as contributors to animal poisonings 86
Unintentional or "indirect" disposal of drugs resulting from use in veterinary practices 87
Drug disposal guidance increasing the hazard of leftover drugs 88
Guidelines for altering, manipulating, or treating drugs prior to their disposal by consumers are ill-advised. 89
Pre-treatment of drugs prior to disposal by healthcare facilities and pharmacies. 92
Occupational hazards of drug waste and relevance to consumers. 94
Pre-treatment of leftover drugs prior to disposal by collection events. 95
Pre-treatment of drugs by encapsulation prior to disposal. 95
Take-Backs; DUMP, DOOP, and RUM campaigns; home and hospital inventories 96
Mail-backs. 99
Role of the CSA. 100
Role of expiry and shelf-life 101
Roles of packaging and medication devices 104
Role pharmaceutical promotions: sampling, detailing, DTC and drug data mining 107
Roles of counterfeiting, importation, and Internet pharmacies 109
Role of donations - and recycling, reusing, reissuing 111
Drug diversion and sharing (possibly made worse by current disposal guidance) 113
Drug disposal for reducing diversion and abuse 117
Drug disposal as a contributor to ambient environmental levels 117
Drug disposal as a contributor to higher episodic spikes of APIs to the environment 120
Proper disposal is not the only approach for reducing ambient environmental levels of APIs 121
Disposal of drugs to landfills 121
Incineration 124
Sustainability/Stewardship/EPR 125

Eco-labeling 129
Biologics 130
Legislative Activities 131
Enforcement activities 132
Antibiotics and selection for antibiotic resistance 133
CONCLUDING ANALYSIS 134
SUGGESTED FOR FUTURE CONSIDERATION 136
GLOSSARY 138
Illustrations pertinent to drug disposal and stewardship (prepared during this project) 140
BIBLIOGRAPHY 153
< END> 196

ABSTRACT

This report represents the first-ever comprehensive examination of the broad scope of issues surrounding the topic of disposal of unwanted, unneeded, leftover medications from consumer use and the countless ways in which the introduction of active pharmaceutical ingredients (APIs) to the environment can be reduced. The report presents a synthesis of thought resulting from the body of work performed on this topic over the last decade by the US Environmental Protection Agency's Office of Research and Development (ORD) at the National Exposure Research Laboratory in Las Vegas, Nevada.

After distilling and synthesizing the published literature, it becomes clear that a holistic solution to the problem of consumer drug disposal will require the coordinated efforts of numerous stakeholders, agencies, and disciplines. A truly sustainable solution has the potential to not just reduce the entry of APIs to the environment via direct disposal of drugs to sewers (by flushing down drains) and landfills (by discarding in trash). More significant outcomes are possible from a holistic, sustainable approach that targets the many factors that contribute to the incidence of leftover drugs. Instead of limiting the focus to mechanisms for disposing of leftover drugs, a sustainable approach could also reduce: environmental loadings of APIs as a result of actions that also minimize their excretion; the incidence of drug diversion and abuse; the incidence of morbidity and mortality resulting from unintended poisonings (for humans, companion animals, and wildlife); and healthcare costs. Perhaps most importantly, a system that minimizes drug wastage may lead to improved therapeutic outcomes and general health, as well as to improvements in other aspects of the system of healthcare such as the way in which drug donations are handled.

It is clear that the most practical and effective potential solutions to the related issues of leftover medications and pharmaceutical residues in the environment reside with the prescribing and dispensing communities and allied industries such as manufacturers and insurers. Countless improvements to these practices could be made, resulting in lower drug usage, fewer leftovers, improved therapeutic outcomes, and lower healthcare costs. This is where efforts need to be focused in changing the behaviors and practices of those involved with medical care. While patient expectations play a large role as well (such as with non-compliance to medication regimens, or with misguided expectations that a successful visit to a doctor is measured in part by whether a prescription is obtained), these expectations need to be changed by the medical care community. The responsibility of manufacturers not only can target issues such as patient non-compliance and excessive or unnecessary drug usage, but it can extend beyond the point of drug usage to deal with leftover medications.

A fully integrated, sustainable approach to optimal drug use and generation and disposition of wastes can only be achieved by the close and integrated collaboration of healthcare professionals, environmental scientists, regulators, and numerous other organizations and stakeholders.

This report seeks to summarize the many facets and nuances surrounding the drug disposal issue in a way suited for informing development of future guidance or regulation. A comprehensive examination of the many dimensions of drug wastage is critically important because policy or regulation not sufficiently grounded with a holistic, systems-level understanding of the overall issue could result in: increased healthcare costs (e.g., increased dispensing costs), poor therapeutic outcomes (e.g., from degraded patient compliance), increased costs to society from policies that exacerbate drug diversion and accidental poisonings, and at best nominal improvement for the environment (if disposal proves to be of little consequence to overall environmental residues of APIs).

INTRODUCTION

A single quotation from Richard Asher (regarded as one of the preeminent medical thinkers of the 20th century) in 1972 serves to capture the bare essence of the life cycle of pharmaceutical products:

"If you give a man a pill there are only two things he can do with it:
he can swallow it or he can throw it away" (as quoted by Taylor 1978).

From this simple beginning stems the vast, inter-related complexities that surround the controversies and consequences involved with the pharmaceuticals we use - and those we fail to use. But Asher's quip omits some of the other, less-obvious detours along a pill's journey. These include: refusing to take the pill, ignoring its usage instructions, giving it to someone else, failing to store it safely (resulting in its theft or deterioration), or simply forgetting about it (until it expires). All of these contribute to the innumerable issues involved with drug ingredients as environmental contaminants and with the unintended problems resulting from their use, non-use, misuse, and abuse. The unintended problems and their possible solutions are the subject of this report.

The focus of this report is on the many issues surrounding the disposal of consumer-generated drug waste. Parallel problems derive from the use of pharmaceuticals by healthcare facilities, as well as by veterinary practices and other professions using pharmaceuticals, such as agriculture. But the issues facing healthcare facilities regarding drug wastage often differ from those for consumer drug waste in a number of ways. For example, the types of drugs used most frequently can differ dramatically; a complex array of regulations govern how drug waste should be handled; and the geographic distribution of healthcare facilities is more limited (making their contributions of drug ingredients to the environment less ubiquitous but also less disperse). Despite the differences with consumer-generated waste, this report discusses some of the aspects of healthcare waste when they are pertinent to consumer use.

A cursory examination of this report quickly reveals the extraordinary complexity of the topic - one with myriad interconnections and feedback loops. Changes designed to improve one aspect can adversely impact others. Countless factors contribute to the accumulation of leftover drugs, which later require disposal. Available options for consumer disposal have yet to prove satisfactory with respect to environmental impact or cost. The extent to which drugs become waste (and the eventual entry of their active ingredients to the environment) is intertwined with the effectiveness of healthcare. Indeed, drug waste is a direct measure of the efficiency and success of the overall healthcare system. Effective solutions will require a concerted transdisciplinary, holistic, systems-level approach - one that integrates the needs, ideas, and expertise of all stakeholders - including environmental regulators, healthcare professionals, dispensers, manufacturers, healthcare insurers, and a broad spectrum of technical disciplines and federal/state agencies. These groups represent a wide spectrum of professions that have never before had reason to communicate or collaborate with one another.

Current approaches for protecting the environment from drug residues are sometimes at odds with protection of human health and safety. Some causes and potential solutions are surprising and counterintuitive – and frequently, deceptively complex. A sustainable solution will instead

need to treat the environment and the patient as an integral whole. The ultimate objective will be redesigning parts of the healthcare system to minimize the accumulation of leftover medications, thereby reducing or eliminating the need to dispose of waste. The concepts underlying the “green pharmacy” (Daughton 2003a; b) and pharmEcovigilance (Daughton and Ruhoy 2008a) would need to play major roles.

Active ingredients in pharmaceuticals (as well as illicit drugs) are now widely established as ubiquitous contaminants in the environment. Beyond the expected occurrence of permissible residues of certain agricultural drugs in food products, their unintended presence has been documented in a wide spectrum of environmental compartments and matrices long known to carry legacy pollutants, including: sewage, surface waters, ground waters, sediments, drinking waters, marine environments, sewage sludge and biosolids, tissues of crops and native vegetation (when biosolids or treated wastewater are used for irrigation or as soil amendments), tissues of aquatic organisms, and even air.

The active ingredients from medications and other pharmaceutical preparations can pose risks beyond those associated with their intended uses in therapy, diagnosis, or prophylaxis. These unintended risks comprise two major categories: (1) introduction to the environment as trace contaminants by the combined actions and activities of myriad individuals, resulting in chronic ultra-low-level exposure for wildlife and humans (e.g., via recycling in drinking water and fish), and (2) their involvement in exposure to wildlife and humans at acute doses, primarily from special situations involving imprudent disposal and from either accidental or purposeful ingestion by individuals for whom the medications were never intended (i.e., drug diversion).

Each of these two major categories comprises several sources or origins. Active pharmaceutical ingredients (APIs) enter the environment by way of: (1) the excretion of unmetabolized APIs (as well as reversible products of metabolism such as conjugates), (2) release from the skin during bathing (from medications applied topically to the skin and from residues excreted through the skin via sweat) (Daughton and Ruhoy 2009a), (3) disposal to sewerage or trash of unwanted, unused, leftover medications, and (4) animal carcasses containing high levels of certain drugs (these tainted carcasses can contain levels of certain APIs that are acutely toxic to animal scavengers) (Daughton 2007). The many pathways by which drugs and their APIs are distributed into the environment and by which they can eventually come into contact with wildlife or result in unexpected, unintended exposures for humans are summarized in two illustrations (also included at the end of this report):

Daughton CG. "Unintentional, Unanticipated Exposure to Drugs [illustration published in: Daughton CG and Ruhoy IS "The Afterlife of Drugs and the Role of PharmEcovigilance," Drug Safety, 2008, 31(12):1069-1082]," illustration, US EPA, Las Vegas, NV, 8 December 2007 (rev 4 June 2008) 2007.

Daughton CG. "The Environmental Life Cycle of Pharmaceuticals [illustration published in: Daughton, C.G. "Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure," In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, San Diego: Academic Press; 2008, pp. 66-102]," US EPA, Las Vegas, NV, December 2006; available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf.

A number of parallels exist regarding these sources with respect to the use of human pharmaceuticals and veterinary pharmaceuticals (especially with regard to confined animal feeding operations, CAFOs); for CAFOs, however, the classes of APIs are primarily limited to steroids, antibiotics, antiparasitics, and anti-inflammatories.

The study of the presence and potential impacts of drugs in the environment encompasses a dizzying spectrum of issues and covers an expansive array of disciplines. It is a transdisciplinary problem requiring collaboration across the fields of not just engineering and science, but also criminology, sociology, psychology, healthcare, pharmacology, pharmacy, health insuring, and politics. The interconnections are so strong that it is extremely difficult to tease any individual aspect apart and discuss or study it in isolation from the others. Articulating an easily understood but comprehensive perspective on this complex, multi-faceted topic has so far eluded all and will certainly not be attempted here. But one outcome from the length and depth of this report may be a better appreciation for the fact that there are no easy solutions to the drug wastage problem.

The focus of this report is instead devoted to just one aspect - the entry of drugs to the environment not as a result of their intended usage (such as from excretion of unmetabolized residues), but rather as a result of their wastage and subsequent disposal. Of the many aspects of active pharmaceutical ingredients (APIs) used in medications and occurring as environmental contaminants, drug disposal continues to capture the attention of the public, the press, the water industry, regulators, and the Congress, which has held several hearings over the last couple of years. In the US, the primary federal agency involvement has been among the Executive Office of the President Office of National Drug Control Policy (ONDCP), the Department of Justice (namely the Drug Enforcement Administration, DEA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA); and the U.S. Postal Service (USPS) has become a recent participant.

With the growing emphasis on recycling and stewardship, numerous options have evolved for the consumer to dispose or even recycle a wide spectrum of items, including pesticides, household cleaners, batteries, electronics (and supplies such as printer cartridges), household appliances, oils, fluorescent lamps (and other mercury-containing items), paper, plastics, cans, glass, packaging materials, and aluminum; for more information see: http://www.epa.gov/epawaste/index.htm. One of the last major classes of consumer items for which a formal, uniform mechanism for disposal or recycling is lacking is that of pharmaceuticals. Pharmaceutical products, however, occupy a unique place in the world of recycling - as they have practically no reuse or reclamation value. Instead, pharmaceutical waste currently represents an economic liability. The real value in drug waste is in the data and information that can be mined from these wastes - potentially useful, for example, in expanding our knowledge of drug effectiveness and the extent of patient non-compliance, both of which play major roles in drug wastage.

But even the specific topic of drug disposal by itself is impossible to cover in a comprehensive manner. While the topic of disposal of unwanted drugs has garnered increasing attention from the public, the pharmaceutical and pharmacy industries, healthcare communities, regulators, and state and federal agencies, comparatively few questions are being asked as to "why is there a medication disposal issue to begin with?" In essence, what factors coalesce to drive the accumulation of leftover medications, creating a consequent need for their disposal? Just about every dimension of the countless factors that feed into the issue of leftover drugs and disposal is complex and surrounded with controversy. This is one of the reasons this problem has proved so intractable and why the focus has been on the comparatively easy part of the problem to solve

(what to do with leftover drugs) as opposed to solving the problems that drive the need for their disposal.

Only recently has an organization involved with pharmaceutical care begun to ask these important questions. The American Society of Consultant Pharmacists (2009a) has stated:

> "Strategies that focus on appropriate disposal of medications do not address the underlying problem that resulted in the waste in the first place. For that reason, strategies that reduce the amount of pharmaceutical waste may be more important and effective in the long run than changing the method used to dispose of unwanted medications. Understanding factors and policies that contribute to pharmaceutical waste is an important first step."
>
> "The first priority should be to reduce the amount of pharmaceutical waste generated, rather than dealing with the pharmaceutical waste once it has been generated. Reducing the amount of pharmaceutical waste addresses the root cause of the problem as well as reducing overall health care costs."

In a resolution adopted by the U.S. Pharmacopeia Convention 4 years prior (USP 2005), the aim had been solely on developing better disposal programs, not on minimizing waste: "to work with appropriate constituencies to continue developing programs to promote safe medication use and disposal"

As a result of our at EPA's Office of Research and Development (ORD) on sustainable pharmacy ("green pharmacy"), we began to formally advocate this approach in 2008 - one aimed at sustainability and pollution prevention (Ruhoy and Daughton 2008). The work reported here results from in-house research performed at ORD's National Exposure Research Program, Las Vegas, beginning in 2003, but primarily since 2006. Major portions of this work resulted from a collaboration with an MD who was being mentored in pursuit of her PhD, which was awarded in 2008 (Ruhoy 2008). As such, valuable insights and perspectives were gained regarding the roles of physicians. This is critical given that most of what occurs within the topic of drug disposal exists at the interface between the environment and health care. This body of work establishes the myriad aspects of how and why drugs become waste materials, how they enter the environment, what the ramifications and consequences can be, and how the wastage can be prevented or minimized. Concerted interest in environmental stewardship and drug disposal first began to emerge after 2003 with development of the concept of the *Green Pharmacy* (Daughton 2003a; b). The first books dedicated to the topic of a green and sustainable pharmacy began to emerge only in 2009 (Bengtsson et al. 2009; Kümmerer and Hempel 2010; Rudén et al. 2010).

The primary focus of this report is on consumer drug use. Analogous problems exist with institutional drug use, but different solutions are often required - largely because of different regulations governing waste handling. An overview of the drug disposal problem in the institutional setting is provided by the American Society of Consultant Pharmacists (2009a). The US EPA has collected substantial data and information regarding the origins and incidence of unused drugs in the healthcare and veterinary sectors (USEPA 2008a; b; 2009), as well as identified best practices for the management and control of unused drugs in the healthcare sector (Lucy and Wu 2009). The EPA is in the process of finalizing guidance for "Best Management Practices for Unused Pharmaceuticals at Health Care Facilities" (USEPA 2010b; c).

For brevity, this report will use the acronym APIs ("active pharmaceutical ingredients") as shorthand for the chemical substances formulated in pharmaceuticals and illicit drugs and which are responsible for the desired or intended therapeutic or lifestyle outcomes. Also note that there are a number of different terms commonly used in discussions of pharmaceuticals, most with subtle differences in meaning; these must be taken into consideration when performing searches of the published literature. In this report, however, these names will often be used interchangeably. In addition to drugs and pharmaceuticals, terms include medication, medicine, medicament, medicinal, and therapeutant; also included in the realm of discussion are diagnostic agents (such as X-ray contrast agents). Generally excluded from this discussion are vaccines and biologics, as these substances (whose structures are based on proteins or nucleic acids) generally do not pose the same types of exposure concerns as ambient residues of synthetic molecules in the environment; there are, however, some possible exceptions, as seen in a published overview regarding biologics in the environment (Kühler et al. 2009).

There are roughly over 1,460 molecularly unique small-molecule APIs registered for use in the US (Wishart et al. 2008), and perhaps hundreds of distinct ingredients commonly used in illicit drugs (Daughton 2010b; Daughton 2011); discussion of the environmental aspects of drugs often must cover both legal and illicit drugs (including counterfeit drugs), as the two groups often have no distinction in terms of chemical composition (Daughton 2010b; Daughton 2011). These small-molecule APIs (biologics are excluded from this discussion) are formulated into over 20,000 parenteral, topical, and oral drug products. The types and relative quantities of these ingredients can vary dramatically across geographic locales - as a function of consumer preferences and prescribing preferences and customs; as an example, for brick-and-mortar US pharmacies in 2009, the number of prescriptions dispensed per capita within states varied 3-fold (from 6 in the west/southwest to 18 in the southeast/northeast), and the total number of prescriptions filled varied 60-fold (from 5 to 30 million) (Statehealthfacts.org 2010a; b). The ambient levels of these chemicals can also vary as a function of the natural processes that dictate their environmental half-lives, such as temperature, pH, solar irradiance, and microbial activity. These products (both over-the-counter [OTC] and prescription only) might be obtained by the consumer or end-user from physicians or veterinarians (by way of prescriptions filled at pharmacies or as free samples), from hospitalization, from stores or Internet pharmacies, from friends (drug sharing), or from the black market.

“Prescription-only medicines" (sometimes abbreviated PoM in the UK) are also referred to in the US as "legend" drugs, which include both non-controlled and controlled substances; at one time the labels for these drugs were required to carry what was called the *federal legend*: "Caution! Federal law prohibits dispensing without a prescription," but which has generally been simplified to "Rx only.” Prescription-only drugs are defined in 503(b)(1)[21 USC §353] of the FD&CA and are essentially those for which adequate directions for self-administration by consumers cannot be provided on a label (USFDA 2009a). Instead, only a licensed prescriber can provide the necessary directions - prior to a prescription being filled; this usually means a doctor, nurse practitioner, physician’s assistant, dentist, or veterinarian. Whether a drug is designated as prescription-only in the US is determined by standards set by the United States Pharmacopeia (USP) and regulated the FDA.

The concentrations of APIs currently detectable in the ambient environment vary dramatically - ranging over roughly 9 orders of magnitude, from sub-parts-per-trillion (ng/L, such as in drinking water) to more than tens of milligrams per liter or kilogram (such as in manufacturing waste streams and in sewage biosolids).

The focus of this report is on the pathways by which APIs gain entry to the environment but which are under direct human control - that is, their release to the environment can be immediately controlled by any number of countless approaches capable of modifying or preventing the actions, activities, or behaviors that lead to their escape or release. These pollution prevention, source control, and environmental stewardship measures can be applied at myriad places along the life cycle of a drug - spanning the chain extending from drug design, manufacturing, formulation, distribution, prescribing, dispensing, and consumption, to eventual disposal of leftovers.

The issue of drug disposal is intimately intertwined with a bewildering array of factors involving society's relationship with drugs, including: manufacturing (e.g., drug formulation), packaging, prescribing practices and customs, dispensing practices (including the health insurance industry), design of drug delivery (especially the need for delivery devices), consumer behavior (numerous behaviors leading to leftover drugs, a major one being problems with patient compliance/adherence), drug collection programs (e.g., take-backs), poisoning (human and animal), diversion, expiry (including stability testing), environmental stewardship, pollution prevention, and legislation, among many others.

With judicious design and implementation of the most effective measures, a more sustainable system of healthcare could be designed. A major aspect of the hypothesis behind this work is that with implementation of measures to reduce the levels of APIs in the environment, significant collateral benefits could emerge for health care, including improved therapeutic or lifestyle outcomes and reduced healthcare costs. The environment and human health are intimately linked. Treating the two as an integral, collective patient holds many advantages with respect to sustainability. In this sense, and of great significance, efforts to control the presence of APIs in the environment are intimately linked with progress toward solving many of the intractable problems long faced by the administration of healthcare.

Traditionally, consumers in the U.S. have used trash receptacles and drains to sewers for medication disposal. Historically (and only up until the last few years), poison control centers have recommended that drugs be flushed down the toilet (whether leading to a septic system or to a municipal waste treatment facility) as the best means of preventing their accidental or purposeful ingestion by those for whom the medication was not intended, especially children. Although disposal to the toilet prevents immediate accidental exposure or ingestion, it unfortunately can add to the overall level of pharmaceutical pollutants in the environment (by way of treated wastewater or sludge). These ambient levels of APIs then hold the potential to lead to extremely low-level, chronic human exposure via contact or ingestion of minute residues in drinking water (as a result of the natural "water cycle") or by ingesting food crops grown on land treated with sludge or irrigated with treated wastewater. With human exposure aside, it is important to note that the entry of APIs to the environment is believed to pose more concerns with respect to exposure by aquatic organisms.

Terminology and What Exactly Is Drug Wastage?

Discussions of drug disposal are complicated enough, but sometimes it is not even clear as to what is meant by the various terms used to describe drugs that are subject to disposal. Terms used in the literature include: unused, unwanted, unneeded, expired, wasted, and leftover. The distinctions between these can be subtle or ambiguous. "Unused" and "expired", for example, are not good descriptors as they only comprise subsets of the total spectrum of medications that can require disposal. “Unused” omits those medications requiring disposal but which have indeed already been used (such as used medical devices). Just because a medication’s container or package have been opened does not necessarily mean it has been "used." "Unused" can also mean to the patient that they are literally no longer using the medication (for its intended purpose), despite the fact that many patients continue using medications on a self-medicating basis (administering the medication for a condition or duration not originally intended - one of many forms of non-compliance). The term "expired" omits the preponderance of drugs that are discarded before expiry - often soon after they are dispensed. The term "leftover" is sufficiently expansive, as it includes all medications no longer being used for the original prescribed condition or intended use - or even unintended purpose.

Another term often used to refer to unused consumer pharmaceuticals is "home-generated pharmaceuticals" (or home-generated pharmaceutical waste); e.g., see: California Integrated Waste Management Board (CIWMB) Criteria and Procedures for Model Home-Generated Pharmaceutical Waste Collection and Disposal Programs (CIWMB -Year Unknown). But this too is not a rigorous term, as many drugs from consumer use are not kept in the home, but are dispersed in countless locations throughout society (Ruhoy and Daughton 2008).

Various acronyms are also used to describe drugs subject to disposal. Some include UEMs (Unused and Expired Medications) and MNU (les Medicaments Non Utilises). Programs designed to collect leftover medications include "take-backs" (often used in the US), and DUMP (Dispose Unwanted Medicines Properly) or DOOP (Disposal of Old Pharmaceuticals) campaigns, which are often used in the EU. All of these terms and acronyms represent but a portion of those needed to perform comprehensive searches of the literature.

A major obstacle in any discussion of drug wastage is what exactly is meant by "wastage." A definition of wastage is notoriously difficult - especially since the topic involves countless variables and perspectives. A simple definition for drug waste is medications dispensed to - or purchased by - a consumer that are never used for the original intended purpose. But, on closer examination, this is not as straightforward as it might first appear. A better term might be "leftover" medications, as this avoids any inference of whether the medications were actually "wasted" (that is, served no purpose). The term "leftovers" does not infer a reason for why medications accumulated unused or unwanted. Would a medication intended for emergency contingency purposes (and now expired) be considered "wasted"? After all, such medications served their purpose of being available for possible emergencies. How about medications intended for unscheduled consumption "as the situation arises" or "as needed" (PRN: "pro re nata," Latin for "in the circumstances" or "as the circumstance arises"). These scenarios show

that it would not be possible to completely eliminate leftover medications - only to reduce them to a necessary minimum.

Development of a "justified definition" of wasted medicines was one of the objectives of a study commissioned by the UK's National Institute for Health Research (Department of Health Policy Research Programme -Year Unknown). This DHPRP project represents the most ambitious attempt to date to capture empirical data on the many facets of drug wastage.

One could ask if the basic premise that medications experience undue wastage is even valid. No one really knows how much drug wastage occurs in commerce (at the consumer level or in the healthcare setting) in terms of either the total quantity or the cost. In one review of medication wastage, White (2010) states that traditional estimates for the UK are that 1-10% of the total cost of medications are wasted; but estimates in the UK are usually based on the quantities of medications returned to pharmacies by consumers, omitting the quantities that are disposed of at home, stored indefinitely, or shared with others.

Many statements regarding drug wastage are based on rates of patient compliance, which is an enormously complex and controversial topic by itself. But non-compliance rates include not just the frequency with which drugs go unused, but also the frequency with which prescriptions are NOT filled or with which they are consumed incorrectly. Neither of the latter contributes to any need for disposal. Failure to fill a prescription may even reduce the need for disposal; so non-compliance does not necessarily lead to leftover drugs. Few make this distinction in the literature. One example is a report from White (2009a), who discusses the many nuances and points of confusion regarding the data on drug wastage.

MAJOR FINDINGS AND INSIGHTS

This project resulted in numerous insights and perspectives. These were used to formulate a wide array of conclusions, findings, and suggestions for future work. Some of these run counter to the consensus or popular opinions that have emerged over the years regarding leftover drugs and disposal. Some even bring into question the validity of new guidance regarding drug disposal. Most reveal complex interplays - where alterations at a specific point of a drug's life cycle can have profound and unanticipated ramifications or adverse actions at other points in the cycle. That alterations at one point in a drug's life cycle can have unintended, unanticipated, or sometimes unrecognized adverse consequences at another is illustrated by the problems faced with opiate pain medications. By limiting the quantities that can be dispensed at one time (to reduce the incidence of leftovers), a patient's continued uninterrupted access to what might be a critical maintenance medication can be jeopardized. Another long-standing example is controls and oversight placed on the prescribing of controlled substances to prevent diversion. An unintended consequence is physician reluctance to prescribe opiates that are critical for controlling pain.

These insights, conclusions, and recommendations represent major findings from this work. These major findings, most of which are interrelated, are numbered but are not presented in any particular order intended to connote importance or priorities. This is because priorities for taking

action would depend on the immediate and ultimate outcomes that are being sought. Though they are presented below under various categories, many are applicable to multiple categories. There are over 40 findings, and nearly all are discussed in more detail in subsequent sections of this document.

Overview

(1) ***The need for prudent drug disposal is not a new issue.*** The accumulation of unwanted drugs in the home and the need for proper disposal to prevent diversion and disposal is not a new problem. Leftover, unwanted drugs have been of interest to healthcare providers and pharmacists since at least the 1960s, when the first studies began to appear in the peer-reviewed literature. Most of the very same concerns and issues discussed today have been under study or debate for nearly 50 years. Other than a more intense concern for potential environmental harm, little has changed. Subjects of investigation over the decades have included: the storage of unneeded drugs in the home, the causes for hoarding medications (such as patient non-compliance), the risks associated with hoarding (such as diversion, abuse, and unintended poisonings), the monetary cost of wasted drugs, and programs designed to collect unwanted medications. To illustrate, the following excerpt is from a paper published over 30 years ago (Goldberg 1977) but which might otherwise seem to be contemporaneous: "The Department of Health is concerned about the increase in cost of supplying medication to patients. Comments have been made in the mass media regarding over-prescribing, patient non-compliance, the high cost of drugs, and the wastage of such medicines." Just the same, drug disposal continues as a concern, and its audience and stakeholders continue to expand. But rather than the widening recognition garnered by drug disposal, what should be surprising is the lack of any real progress toward comprehensive or even simple solutions. Despite the attention that the accumulation and disposal of drugs has garnered over the last 4 decades, there are many unanswered questions - as well as many misconceptions.

(2) ***Drug disposal is a deceptively complex issue and one refractory to simple solutions***. This is borne out by the fact that it has been a point of discussion in the medical literature for over 40 years and by the very length of this report. The factors leading to leftover drugs requiring eventual disposal are innumerable, highly complex, and associated with myriad interconnections, some of which are not at all obvious. The factors dictating how drugs can be disposed vary across countries and even states within the US; some of these differences are in part responsible for the relative lack of progress in the US. The published literature is characterized by an over-wrought focus on drug collection programs (e.g., take-backs), which represent only one aspect of the overall issue. These publications tend to rehash the same points but to overlook some of the key scientific questions.

CAUSES of LEFTOVER MEDICATIONS

(3) ***The causes of accumulation of leftover drugs are numerous, complex, and not amenable to simple solutions***. Two of the major factors long assumed to cause medications to go unused - eventually necessitating disposal - are patient non-compliance

(failure to take medications as directed) and dispensing of purportedly excessively large quantities (such as 90-day supplies). The issue of non-compliance is extraordinarily complex. Efforts to reduce its incidence will not necessarily result in fewer leftovers and in some instances can jeopardize patient health. If any conclusion can be made regarding dispensed quantities, it can only be safely surmised that a number of factors must be considered together with regard to each patient, the type of treatment, and the specific medication being employed. Across-the-board restrictions on quantities dispensed (either more or less) can have adverse consequences for therapeutic outcomes, patient health, and associated costs. Without consideration of the complex interplay between numerous inter-related factors, an assumed improvement in one area can have unforeseen adverse consequences in another. This general problem of unforeseen consequences repeats itself throughout the many facets of the drug disposal issue. This points to the fact that viable solutions may need to be customizable to the individual patient or situation.

(4) ***A comprehensive approach for reducing the incidence of leftovers will require a full and accurate understanding of the entire cradle-to-grave life cycles of medications***. The life-cycles of drugs are extremely complex. This is shown by the network illustrations covering the origin and fate of pharmaceuticals and illicit drugs (also appended at the end of this report):

> Daughton CG. "Illicit Drugs and the Environment [illustration published in: Daughton CG "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology," Reviews of Environmental Contamination and Toxicology, in press, March 2011)]." illustration, US EPA, Las Vegas, NV, 7 December 2009 (rev 17 June 2010) 2009.
>
> Daughton CG. "The Environmental Life Cycle of Pharmaceuticals [illustration published in: Daughton, C.G. "Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure," In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, San Diego: Academic Press; 2008, pp. 66-102]." published illustration, US EPA, Las Vegas, NV, December 2006.

Although many aspects of the complex network of processes spanning manufacturing to eventual waste treatment are well understood, some are not. Patient non-compliance, for example, is a major factor that generates leftovers but whose control is poorly understood. The many forms of manufacturer promotions (such as advertising and free samples) have poorly understood impacts on drug purchase and consumption. Even the distribution and reverse-distribution chains for pharmaceuticals are not fully understood by those outside the industry because some aspects are proprietary; one of the most comprehensive overviews of the reverse distribution system is provided by Kumar et al. (2009).

DISPOSAL: SCIENCE ISSUES & CONCERNS

(5) ***Evidence for drug disposal acting as a major origin of ambient aquatic residues of APIs does not exist, except for some select cases*****. Much of the ongoing effort in developing drug collection programs to divert leftover drugs away from sewers and trash, with the intention to protect environment - lacks a body of supporting data for justification** The question as to what fraction of collective or

individual API residues in the aquatic environment emanates from direct disposal versus excretion and bathing is currently not answerable. The relative contribution from disposal versus excretion probably varies dramatically from drug to drug or from class to class (e.g., antibiotics, analgesics, hormones, controlled substances, etc). It also might vary according to the type of packaging (e.g., bulk containers versus blister packs; with the latter probably discouraging disposal to sewers). Little evidence exists to support general conclusions regarding the potential effectiveness of ceasing drug disposal to sewers (or landfills) as a means of reducing ambient aquatic levels of APIs (or APIs in biosolids). Hypothetically, if all disposal of medications to sewers were to cease immediately, it is possible that there might not be any measurable difference in the current environmental loadings of APIs in general; some differences might be measurable for a limited number of particular APIs. This consideration has been overlooked by nearly all assessments to date of drug disposal, but it represents one of the research needs outlined in 2004 (Daughton 2004). Distinguishing API residues that have originated via disposal from API residues coming from excretion and bathing by chemical monitoring is currently not possible, except perhaps for those APIs that should experience the most extensive metabolism (and therefore are poorly excreted) and whose monitored levels greatly exceed those based on predictions from usage. To date, only two papers have appeared in the peer-reviewed literature that delineate the requirements for determining the relative contributions of APIs to the aquatic environment from disposal to sewers versus excretion. These papers discuss the variables that must be addressed and the types and quality of data required for the calculations (Daughton and Ruhoy 2009a; Ruhoy and Daughton 2007). No study to date has met these requirements.

Even less is known regarding the contributions to the environment as a result of disposal of illicit drugs (Schedule I) and diverted licit drugs. While progress is being made in obtaining more reliable data on the types and quantities of illicit drugs in use (Daughton 2011), almost nothing is known regarding the frequency or magnitude of their disposal. One approach that has been used for assessing recreational drug use is "amnesty bins" at rave parties (Kenyon et al. 2005).

(6) ***Drug disposal may serve as the major source of APIs in landfills (even when not receiving biosolids)***. While consumer-generated API residues in the ambient aquatic environment may or may not be reduced by controlling release of APIs disposed to sewers, disposal is perhaps the major source of APIs in landfills receiving domestic trash. In contrast to the aquatic environment, disposal of medications via household trash represents the only source of consumer APIs in those landfills that are not also receiving biosolids. Paradoxically, comparatively little is known regarding the magnitude of API disposal to landfills or the fate of APIs in landfills. Even though the focus of this document is on drug waste resulting from consumer wastage, worth noting is that hospitals not having a formal pharmaceutical waste program generally dispose of leftover drugs (including new and used devices and containers) in red sharps containers. These are then sterilized by microwaving or autoclaving (which does not destroy most APIs) followed by landfill disposal. This constitutes the other major source of APIs in landfills.

(7) ***Disposal to trash poses unknowns with regard to the environmental fate of APIs.*** Current guidance recommending disposal of unwanted medications to domestic trash destined for landfills poses additional concerns, other than increased risks for diversion and poisoning. Landfills are not intended for, nor are they capable of, effecting rapid and significant chemical transformation of synthetic organic chemicals into simpler structures that are environmentally benign. The drug residues that accumulate in landfills have the potential to eventually be transported to leachates. When these leachates are actively collected and diverted through an engineered design to a waste treatment facility or if portions eventually migrate to groundwater or surface water via defective engineered barriers, they can eventually contribute to the total environmental load.

(8) ***Disposal to trash poses additional hazards.*** Guidance for disposal to trash usually recommends removal of personal information and/or removal of the identity of the medication (to discourage diversion). Should a poisoning then occur, emergency personnel no longer have access to potentially vital information on the drug's identity, postponing diagnosis and initiation of treatment.

(9) ***Concerns regarding individual privacy during disposal can increase the risks for poisoning or injury.*** General concerns regarding protection of personal information – sometimes motivated by the Health Insurance Portability and Accountability Act (HIPAA) - play roles in disposal guidance or regulations. Privacy concerns pose a conundrum when medications are tossed into the trash. Many labels are impossible to remove from their containers. Although it is wise to remove personal information from labels prior to disposal, removing all identifiers from a label, such as the drug name, dosage, dispensed quantity, and dispensed date could hinder medical measures needed in the event of an unintended poisoning. Additionally, disposal guidance that encourages the consumer to deface or obliterate information on the label may not accomplish its goal, as label print is notoriously difficult to obscure with black ink, and covering with tape provides only a cosmetic solution, as it could be easily removed. Some consumers might therefore resort to physically obliterating the label, for example by attempting its removal with a razor blade, which poses risk for laceration. Redesign of labels to separate manufacturer data from personal information so that the portions containing only private data would remain affixed to containers under extreme storage conditions but could be easily removed when desired would be extremely useful in solving these problems.

UNDER-RECOGNIZED CONCERNS or DRUG-USE PRACTICES

(10) ***Graywater and septic systems are under-recognized potential problems with regard to drug disposal***. APIs (especially antibiotics and biocides), when disposed to drains feeding septic systems, may have the potential to disrupt wastewater treatment more than with centralized waste treatment systems. Furthermore, the occurrence of APIs in graywaters could pose concern with regard to on-site reuse/recycling (e.g., such as for land application/irrigation); graywater is household wastewater originating from all domestic plumbing fixtures except toilets. Surprisingly, little is known regarding the API content of graywaters, but clearly the composition is a

direct function of the medications used in each specific household; each household, therefore, has the ability to control the contaminants entering its own waters or to alter the reuse of its graywater (e.g., reuse for toilet flushing but not for irrigation). Some of the only studies that have examined or discussed API occurrence in graywaters include: Eriksson et al. (2003), Eriksson et al. (2009), Maimon et al. (2010), Kvanli et al. (2008), Almqvist and Hanaeus (2006), Andersen et al. (2007), and Donner et al. (2010). An examination of personal care products in graywater was made by Leal (2010).

(11) ***Disposal of certain select delivery devices to sewers may serve as a major source of particular API residues in the environment***. A particular class of medications for which evidence supports the possible importance of disposal to sewers as a source of APIs in the environment involves both used and new delivery devices, especially transdermal devices (e.g., patches). For example, when flushed, new dermal patches containing methylphenidate can contribute the equivalent amount of API as from excretion resulting from 3,280 oral doses; patches containing ethynylestradiol can contribute the equivalent of 214 doses (Daughton and Ruhoy 2009a).

(12) ***Pharmacokinetics, dosage form, and patient compliance are the main factors dictating whether disposal can be a significant contributor to ambient environmental levels of APIs.*** The biological and chemical processes that act upon an API once it enters the body, including those effecting absorption, distribution, metabolism, and excretion are all part of the scope of study called pharmacokinetics (PK). For those APIs that are extensively excreted unchanged (i.e., they undergo little metabolic alteration or tend to be excreted as reversible conjugates) or for those formulated into medications that have unusually high rates of patient compliance (which results in proportionately few leftovers), disposal to sewers may only contribute immeasurably small increments to total environmental loadings. On the other hand, for those medications containing APIs in transdermal devices and not generally used in oral or topical dosage forms, their disposal to sewers could serve as the major or only source of API residues in the environment; examples include rotigotine, flurandrenolide, and lidocaine. Pharmacokinetics, exclusive dosage forms, and patient compliance are three critical variables that must be known to assess the potential for aquatic impact of each individual API disposed to sewers; these have been covered by Daughton and Ruhoy (2009a), who present a rather comprehensive overview of the many factors involved with excretion in general and the role played by pharmacokinetics.

(13) ***Certain drug-use practices can essentially serve as indirect, unintended, hidden forms of disposal.*** There are at least two ways in which drugs are used as intended but which ultimately serve as alternative pathways of unrecognized disposal. One involves drug-laced carcasses of animals just treated with large doses of certain drugs. Improper disposal of these carcasses can result in acute (and often fatal) exposures for scavengers that then consume the carcasses. A second involves the common practice of application of certain drug preparations directly to the skin. Most of a topically applied API is not absorbed by the body and is instead washed directly into sewers or waterways during bathing. APIs in these topical preparations are present at relatively high levels (e.g., the milligram-per-gram or percent range - known as "high content" preparations),

so one dose applied to the skin can release as much API to sewers as excretion from hundreds or thousands of oral doses after metabolism. Even if the disposal problem were completely solved, the direct introduction of large quantities of certain APIs to sewers would therefore continue simply as a result of intended use (Daughton and Ruhoy 2009a). This means that other forms of pollution prevention would be required - namely changes ranging from drug formulation or delivery mechanism, to patient behavior (how and how much medication is dermally applied). Many topical drugs have traditionally been applied at very large excessive doses - by covering more of the skin than needed with larger amounts than prudent. This has been recognized as a clinical problem for quite some time - and also recognized as a cause of leftovers (Savin 1985).

(14) ***Biologics pose little concern with regard to disposal to sewers, but do pose some concern with regard to disposal to trash***. Biologics comprise a broad and continually expanding class of pharmaceuticals - with chemical structures based on proteins, nucleic acids, or sugars - and are used in vaccines, gene therapy, and other modalities not conducive to conventional "small molecules." These substances are often unstable in heat, light, and air, and generally unstable in the gut or inefficiently absorbed from the gut (the entire system of digestive organs). In general, biologics do not pose the conventional concerns associated with small-molecule pharmaceutical disposal. Those that do get excreted - and even survive sewage treatment and environmental transformation or structural 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. Although no published evidence points to concerns that might be associated with disposal to sewers, disposal to trash may pose unknown risks should someone unintentionally or unknowingly consume them orally or contact them with their skin, as the possibility of allergic reactions exists. Whether biologics pose concerns, certain additives may. An example is the organomercury preservative thimerosal, which is used in certain vaccines and other biologics (PharmEcology 2010).

(15) ***Drug donations are a major problem for humanitarian relief efforts*.** In general, consumers should always be discouraged from donating pharmaceuticals to relief efforts; many countries do not welcome donations even from manufacturers. Humanitarian relief efforts often attract hundreds or thousands of tons of unwanted, unnecessary, inappropriate, or expired medications. Having to store and manage such huge inventories (which can amount to thousands of tons of drug waste) diverts resources from important activities and later imposes enormous costs for disposal or site remediation. As a consequence, the international guidelines for drug disposal issued by the World Health Organization (WHO 1999 [revised]) could be integrated into national drug policies worldwide. Drug donations could be regulated as both a public and environmental health issue. Alternatively for the US, one or several agencies could issue clear guidance (patterned after the guidance issued by (WHO 1999 [revised]) to ensure that pharmaceuticals originating in the US do not become a burden for other countries. Ultimately, disposal practices should abide by the *Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal* (Basel Convention

1989), which is the most comprehensive global environmental agreement on hazardous and other wastes; it contains language specific for pharmaceutical waste. Its signatories are expected to minimize waste transported across borders and to minimize the quantity of waste generated as well as the distance between the location of waste origination and eventual disposal.

DISPOSAL GUIDANCE

(16) ***Guidelines for prudent disposal need to avoid a singular focus on protecting the environment.*** Guidance recommending the continued disposal of a limited number of certain medications to sewers is amply justified by the acute risks posed by disposal to trash. Unintended or purposeful exposure via ingestion or dermal contact (especially by infants, toddlers, and pets) to these medications can lead to significant morbidity or mortality. A better balance of concern is required when developing disposal guidelines. Absent comprehensive disposal options usable by all the public, highly toxic drugs will probably continue to require disposal to sewers. Redesign of drug disposal practices to better protect the environment needs to take better note of the need to protect human safety. A methodology to determine whether continued sewer disposal of any particular API might be a major contributor of its environment occurrence was developed by (Daughton and Ruhoy 2009a).

(17) ***Current drug disposal guidance may be flawed and increase risks for humans.*** Current guidance on disposal of drugs to domestic trash poses documented hazards to the safety of humans, pets, and wildlife. In particular, guidance specifying the physical destruction of hard dosage forms (e.g., crushing tablets) poses acute risks for those following the guidance as well as for those who might be incidentally exposed to any particulates or dusts that might escape within a home or to doses that might be unknowingly spilled onto floors or other surfaces accessible to infants, toddlers, or pets. Certain medications are specifically designed to resist mechanical alteration/destruction. Reclaiming discarded drugs from trash may increase the incidence of diversion and acute poisonings for humans as well as for wildlife scavengers. Discarded transdermal devices (e.g., skin patches) pose particular risks, especially for children, who may chew or swallow them, or apply them to the skin. Some transdermal devices containing synthetic opioids, for example, hold lethal doses for those who are opiate naive. This points to the critical importance of continuing the practice of disposal to sewers for certain, select medications. Drug disposal programs (such as take-back or collection events) can exacerbate another known hazard simply by encouraging consumers to set aside their leftover drugs while waiting for sufficient quantities to accumulate - to justify making a trip to turn them in at a collection event. This behavior could result in the temporary stockpiling of extremely hazardous, leftover drugs. This could increase the potential for poisonings - simply because more types and higher quantities of drugs remain on-site than might ordinarily if disposal were performed immediately.

Exposure to certain leftover drugs is also extremely hazardous for particular sub-populations, especially those who need to actively avoid them. Examples are drugs under restricted distribution programs or potential teratogens, such as isotretinoin, thalidomide,

tamoxifen, methotrexate, and finasteride, which must be avoided by women of child-bearing age.

The involvement of drugs as a major cause of human poisonings, especially children, makes drug disposal a priority for the Agency. Administrator Lisa Jackson, in an all-employee memo of 16 March 2010 ("EPA's Leadership in Children's Environmental Health") reiterates that protecting children's environmental health is central to EPA's work. The memo cited three key areas of focus, one of which is protection of children through safe chemicals management:

> "I named chemical management as one of our top priorities for EPA's future largely because of the disproportionate effects of chemical exposures on children. We will establish standards, policies and guidance at home and abroad that help eliminate harmful prenatal and childhood exposures to pesticides and other toxic chemicals. We will work with Congress and stakeholders to identify effective approaches for the protection of children's health in the context of TSCA reform. We will also encourage green chemistry and safer alternatives to chemicals and products that present a potential hazard to children."

(18) ***Drugs possessing the potential for single-dose lethality require special consideration in disposal guidance.*** Very real acute poisoning risks are posed by improper disposal of drugs having single-dose fatal toxicity potential for children; included as extreme hazards are certain transdermal and other drug delivery devices (e.g., medicated patches). Drugs having single-dose lethality are of special concern in the practice of medicine and pose such a significant hazard for those not intended to receive them that they warrant special emphasis here. As one of many examples, after 3 days of use, fentanyl patches can retain up to 84% of their original fentanyl content, a more than sufficient fatal oral dose for an infant or fatal dermal dose for an opioid-naive adult (Marquardt et al. 1995).

(19) ***Protecting the environment with optimal disposal guidelines can conflict with ensuring human safety.*** A major dichotomy regarding disposal is that flushing can directly impact the aquatic (and terrestrial) environment, while discarding in domestic trash can directly impact human health and safety. Neither is a good option. The need for prudent drug disposal has been driven by the sometimes opposing needs to protect the environment (by minimizing the discharge of APIs to sewers) and protect human health and safety (by reducing diversion and unintended poisonings). These two needs (primarily the second) were the drivers behind the first federal guidance for drug disposal, implemented by the ONDCP with assistance from the FDA and EPA in 2007 (ONDCP 2009 [updated October]). But the published evidence is sparse that supports the claim that leftover, unwanted medications stored in homes and awaiting disposal is a major contributor to diversion and poisonings. This is because the portion of diversion and poisonings resulting from unwanted, leftover drugs cannot be teased apart from that resulting from medications that are in current use as intended. In general, investigations of poisonings do not report how a victim encountered a medication; there is no way to discern whether the medication was being actively used by the intended recipient, or

stored for future use, or stored for eventual disposal, or discarded in trash, or simply laying around the home long-forgotten.

(20) ***Prudent drug disposal requires balancing the protection of the environment with ensuring access to timely medical care.*** Any plan to promote what might be called "prudent" drug disposal must strike a difficult balance in meeting three major objectives: (i) protecting the environment, (ii) maintaining human safety (e.g., guarding against diversion and unintended poisonings), and (iii) ensuring that patient access to critical medications is not impeded (in particular, controlled substances for control of pain). Should one of these objectives become over-emphasized, one or both of the others can be jeopardized. The best example is the balance needed in preventing diversion of opiate analgesics while at the same time not discouraging or hindering physicians in prescribing controlled substances to patients seeking pain control.

FORMAL COLLECTION PROGRAMS

(21) ***The potential effectiveness of drug-collection programs for curbing imprudent disposal is unknown***. Even if nationwide approaches were available for collecting leftover medications (such as take-back programs), a major unaddressed question is what portion of the public would routinely make use of them; limitations or concerns that have been expressed by consumers include inconvenience, insufficient time, privacy concerns, preferences for alternative routes of disposal (such as flushing), and skepticism as to the seriousness of the disposal problem. Even in countries with long-established take-back programs (such as the UK), only a minority of the public makes use of the service (e.g., see: Bound and Voulvoulis 2005). A few have voiced reservations regarding the usefulness of collection programs; two examples are Morissette (2006) and Mackridge (2005).

(22) ***Formal collection programs for unwanted drugs may have significant hidden costs.*** Unexpired medications represent not only unrecoverable purchase costs for the consumer, but more importantly, they often represent lost opportunities in achieving the intended therapeutic outcome. Another example of hidden cost is the collection of unused antibiotics; consumption of partial treatment regimens can encourage the emergence of antibiotic-resistant pathogens, a cost borne society-wide. Many other costs are associated with collection programs, including costs associated with transportation by the consumer and collector, as well as time and effort.

(23) ***The statistical representativeness of data from drug collection or take-back programs is unknown.*** The types, quantities, and rate or frequency of return of unwanted drugs turned in during drug collection programs cannot be assumed to represent trends that can be extrapolated. There are currently too many unanswerable questions. A number of factors must be known to determine how statistically biased the collected data might be. Are the participants representative of the population at large? Can the data be used to extrapolate across the broader population and over time? Would the collection data be representative of return rates sustained over longer periods of time?

Do drug collection events preferentially attract those who are motivated and who have stockpiled their unused drugs over long periods of time until they locate an opportunity for disposal? This last phenomenon could result in a consumer returning relatively large quantities of drugs that had been accumulated or stockpiled over the course of many years and yet be misinterpreted as a quantity that would continue to be returned on a periodic basis. This makes it very difficult for drug collection events to use acquired data to predict future return rates. Collection events are also prone to biased data as a result of selecting for those consumers who are willing and able to participate. It is unknown what percentage of the general population these individuals represent. This is self-selection bias.

With a few exceptions, the data that have been collected are largely unusable because of the basis for their measurement. The first study to present a comprehensive summary of accumulation/disposal data acquired from a well-defined sub-population of a single city over the span of a year was published in Ruhoy and Daughton (2008, see Table 3). This study made use of the comprehensive and accurate data residing in coroner records, an approach pioneered by Ruhoy and Daughton (2007); note, however, that coroner data on unused drugs can vary across states and is therefore not always an options for study. Studies collecting data on drugs returned to pharmacies use two basic approaches: (1) return events that advertise in advance and (2) those that make use of existing returns programs that are not advertised. The latter unsolicited collections may yield less-biased data. Their rates of collection and types of collected drugs may be more representative of what could be obtained in sustained real-world routine collections from the general population; note, however, that this type of study has only been done in other countries having on-going collections programs - generally operating through pharmacies.

(24) ***Data from drug collection programs cannot be inter-compared; standardization is needed*****.** Data collected from most drug take-back programs cannot be inter-compared in any way useful for environmental modeling or for assessing the potential for environmental impact or estimating drug usage/wastage. This is because of a lack of standardization on exactly what is being measured as well as the actual units of measure. Drug collection programs attempt to quantify their success by using widely different approaches for measuring and reporting the quantities of collected drugs. The most common shortcoming is the failure to report what exactly is being measured and the units of measurement. For successful comparisons between collection programs, for scientists to use the data for predictive modeling purposes or for environmental assessment, it is essential that the units of measurement be defined. A range of approaches are used by these projects and often are not even specified. The measures usually employed include the mass of the entire formulated medications themselves (e.g., tablets and capsules, including all inert ingredients or excipients), the mass of the complete formulated medications plus their consumer-use packaging, the mass of medications plus packaging and shipping containers, or simply the rough volume. With few exceptions, such as the State of Maine's mail-back program (Kaye et al. 2010), the mass of each dose (and API) is rarely recorded. These disparate measures will obviously yield wildly different values (which can vary over many orders of magnitude). In one study, for example, packaging materials were found to compose more than 90% of the

total weight of collected materials; and of the remaining 10%, only 1-2% actually comprised APIs (Macarthur 2000).

The only single measure that has some relevance with regard to ecotoxicology and human health is the mass of each individual API. But recording inventories on the basis of each dose collected, followed by performing the required calculations to convert to API masses is a very time-consuming and laborious task; the first (and still one of the only) publications to actually calculate the mass of individual APIs that were disposed was published by Ruhoy and Daughton (2007). A standardized approach would be extremely useful for measuring, cataloging, and grouping APIs. One approach would be to use an international standard for categorizing the APIs according to their action on therapeutic systems, such as the Anatomical Therapeutic Chemical (ATC) Classification System. An example using this approach is presented in Ruhoy and Daughton (2008, see Table 3).

A good example of this problem derives from the New Jersey Operation Medicine Cabinet collection, which may have been the largest collection to date in the US. Collected were over 9,000 lbs with a street value of over $35M (DEA 2009a). While the 9,000 lbs comprised 3.5 million pills, it was not specified whether this was the mass of the packaged pills or the pills alone. Even if it were the pills alone, the collected quantity of actual APIs would be nearly 6 orders of magnitude lower. If the average API content of a pill were assumed to be 100 mg (many medications are 20 mg and below), then the collected amount of actual APIs would have amounted to 350 kg. While this is certainly a significant quantity of active ingredients, the reported data (9,000 lbs) mis-represents the environmental significance of the collected drugs. Worse yet, if the 9,000 pounds included packaging, then the collected mass of APIs was much lower yet (by two or more orders of magnitude).

But it is critical to recognize that even measures of mass will become increasingly less useful as the potencies of new drug entities increase. Clearly, the total mass of the entire formulated dosage form imparts little knowledge regarding the mass of the constituent APIs, when the APIs can range in dose from the low micrograms up to hundreds of milligrams - 5 orders of magnitude. It is rather pointless to compare the success of one take-back event versus another on the basis of weight collected, as this cannot impart any meaning with respect to even the relative masses of the APIs, or more importantly, their biological potencies.

In the final analysis, the major rationale for performing detailed inventory and examination of unwanted, leftover medications collected during take-backs is to derive data regarding prescribing, dispensing, and consuming. These data could prove invaluable is designing adjustments in the system of healthcare. Improvements would be aimed at optimizing the interconnections among all three of these aspects of the life cycle of drugs, so that usage is more efficient - resulting in less cost and better healthcare endpoints. Studies of returned or collected drugs are important perhaps not so much to assess their potential contributions to environmental contamination but rather to improve the delivery and quality of healthcare, including the prevention of accidental poisonings,

diversion, and adverse drug events. Also worth noting is that inventory of collected drugs could potentially assist in spotting counterfeit drugs – perhaps offering early warnings of their introduction into the supply chain.

(25) ***Prudent drug disposal requires attention not just to the API, but also to the packaging***. Do the packaging materials (especially bottles and dispensers containing concentrated residuals of APIs) or the ever-increasing numbers of delivery devices once they have been used (e.g., delivery devices unique to certain drugs such as pumps, dermal patches, inhalers, syringes) pose a significant source of certain APIs? The continued development of advanced delivery devices (e.g., with the further integration of electronics) will complicate disposal yet further. Does packaging constitute a significant source of other pollutants derived from the packaging itself (e.g., via incineration or weathering in landfills)? Could these problems be controlled by redesign of the packaging or by alternative disposal methods? Are the known extractables and leachables within dispensing devices and containers themselves a significant source of certain pollutants in the environment (e.g., plasticizers, nitrosamines, and acrylonitrile, deriving from plastics adhesives, antioxidants, coatings, vulcanizers, accelerants, adhesives)? An example of one major class of commonly used devices (i.e., Orally Inhaled and Nasal Drug Products - OINDP), such as inhalers, could eventually pose special challenges as electronics become integrated with the device. Perhaps the best stewardship model for electronic OINDPs or other sophisticated delivery devices could be the electronics industry, where the used product is returned to the manufacturer, who then disassembles the device and reclaims or detoxifies the constituents. Little data exist on the significance of either unused or partially used OINDPs in drug collection events; the work of James et al. (2009) is one of the only examples.

(26) ***Drug collection programs (e.g., take-backs) may not be an effective approach for reducing the diversion of the primary drugs of concern - controlled substances***. Very little study has been directed to determining the relative rates of return during take-backs of controlled substances or drugs of abuse versus those for non-controlled substances. One study (in Sweden) showed a much lower rate for drugs of abuse compared with other drugs. This may have been due to the intrinsically higher rates of hoarding or diversion for non-medical use (Ehrling 2005).

(27) ***Patchwork of take-backs in the US adds to the existing confusion regarding drug disposal***. The growing number of local, regional, state, and most recently national efforts designed for collecting leftover drugs is confusing on several levels. These efforts range from one-time sporadic events to ongoing programs. The major source of confusion is whether controlled substances are permitted. This is a function of whether law enforcement or the DEA is formally involved. Without their formal involvement, controlled substances cannot be collected. The consumer, however, often does not know how to determine if a drug is a controlled substance. Criticism of the status quo regarding the handling of leftover drugs has been increasing. One example comes from Barthwell at al. (2009a):

> "The U.S. government, the pharmaceutical industry, medical practitioners, and waste disposal authorities have yet to develop a consistent message or systematic method for consumers to

> properly dispose of pharmaceutical products. The only advice on disposal currently available to consumers is to mix old medications with cat litter or coffee grounds to make them unpalatable before throwing them away. The U.S. Food and Drug Administration, the U.S. Drug Enforcement Administration (DEA), and the U.S. Environmental Protection Agency – under the coordination of the Office of National Drug Control Policy – must improve this rudimentary, insufficient approach."

(28) ***Sustainable approaches to drug disposal require clear and useful measures of success***. A major unmet need with all approaches for collection of leftover drugs from the public for disposal (such as by take-backs) is the articulation of clear measures of success. For any collection program to ever declare success, the performance goal(s) needs to be clear and measurable. Historically, collection programs invariably focus solely on collecting and destroying unwanted drugs. At best, the only measure of "success" has usually been the documentation of the total mass or volumes of collected products (usually including the packaging or the inert ingredients, which comprise the bulk of a dose). But these measures do not address outcomes. Few studies have ever attempted (and none has ever succeeded) in linking drug collection programs to either reductions in ambient environmental residue levels or to reductions in human poisonings (either unintentional or purposeful). Furthermore, measuring gross weight and volumes is not well suited to comparing effectiveness among different programs; it is useless for predictive modeling, where the content of the individual APIs must be known. There are three major measures (outcomes) for assessing whether a drug disposal program is successful: (1) Reduction in accidental and purposeful poisonings (both humans and domestic pets); (2) reduction in ambient levels of individual APIs in various environmental compartments (primarily sewage influent, sewage effluent, waters receiving sewage effluent, sediments, sewage sludge/biosolids, and drinking water); and (3) improvement in various outcomes from, or activities practiced in, the administration of healthcare; two examples are improved prescribing practices (by mining data associated with the types and quantities of collected leftover drugs) and improved therapeutic outcomes for patients. All three of these measures would face formidable challenges in their assessment. A necessary conclusion, therefore, is that drug disposal programs in all likelihood can be implemented usually only as a precautionary action. But while there is little hope in the near future for assessing their true effectiveness with respect to environmental impact, the emphasis on drug collections in the US has had recent impact on pharmacy policy, with the facilitation of shorter-term dispensing for certain drug classes.

DRIVERS for ASSESSING MEDICATION WASTE

(29) ***Connection to Healthcare: Viewing leftover drugs as measures of success or opportunities for improvement, rather than simply as waste*****.** A new paradigm is proposed for medication usage. This paradigm seeks to solve the disposal issue while at the same time minimize the use of resources. Leftover, unused medications should be viewed not as chemical waste but rather as measures of wasted healthcare resources and as opportunities lost for achieving intended therapeutic treatments. Leftover medications represent the nexus of numerous facets of the healthcare system and patients' complex relationships with drugs. The very fact that the issue of drug disposal

has grown to such proportions amply demonstrates that there may be areas needing improvement in the healthcare system. Drugs are not always being administered in an efficient/efficacious manner, patients are ignoring instructions, or the medications are not efficacious or have too many adverse effects. By redesigning and optimizing the use of medication, the need for disposal can be minimized. Further, by implementing systems that can readily inventory the types and quantities of leftover medications in a central database, alterations can be made to prescribing and dispensing practices that could reduce the incidence of leftovers while also improve healthcare outcomes. Beyond their potential to be discarded and enter the environment as contaminants, leftover drugs are serving as messengers of potentially critical importance to the state of the healthcare system - and serve as indicators of the many ways in which this system could possibly be improved. Although the need for waste collection of unused drugs has been justified primarily as a means for reducing diversion, abuse, poisoning, and environmental contamination, it has not yet evolved to take advantage of two potential avenues: reclaiming valuable chemicals (i.e., APIs) for their reuse or re-purposing, and the mining of extremely valuable information for better targeting the administration and cost-effectiveness of medical care (e.g., answer questions to improve prescribing, dispensing, patient compliance/adherence, or to advance evidence-based medicine). Leftover medications should not be viewed just as nuisance wastes, but rather as tools useful for gauging the effectiveness and efficiency of medical care. In general, leftover medications are indicators or measures of two conditions in the administration of healthcare: (1) prudent and efficacious medication is not being properly used (non-compliance/adherence), and therefore the targeted therapeutic outcomes are not being achieved, or (2) unnecessary medication from imprudent or unnecessary prescribing is not being consumed as the prescriber intended because the patient senses the medication does not work or is responsible for adverse drug reactions (ADRs).

(30) ***Focus on Source Reduction: An overwrought focus on drug disposal may distract from a sustainable solution yielding a wide range of collateral benefits.*** A current narrow focus on developing what might initially appear to be better means of disposing of unwanted drugs may be detracting from the far more important objective of reducing the occurrence of leftover medications in the first place. Attempting to control disposal is an inefficient way to tackle the overall problem of APIs in the environment. The complex chain of actions, activities, behaviors, and customs involved with all aspects of the life cycle of medication use in health care inevitably leads to leftover medications. Redesign of key places in the life cycle holds great potential for not only reducing the incidence of leftovers, but also leading to improvements in the quality and cost of health care. The potential for collateral benefits of significant cost savings and improved health may become a major driving force behind the need for comprehensive environmental stewardship programs directed at drug use. For this reason, a major conclusion from this report is that the focus of efforts addressing the issue of drug waste needs to be on solutions for minimizing the generation of waste at the outset rather than on how to handle it once generated - - up-stream pollution prevention and stewardship practices as opposed to down-stream mitigation measures. The objective should be reducing the quantities of medications that go unused rather than figuring out how to dispose of medications whose accumulation could have been prevented. *The ultimate*

objective should be to eliminate the need for avoidable disposal altogether; the need for a certain degree of disposal will always be needed, such as for the stocks leftover from the deceased. This can be done only by collaboration among environmental scientists, the healthcare communities, pharmaceutical and pharmacy industries, and the health insurance industry. This point of view began to be formalized only in the late 2000s (e.g., Daughton and Ruhoy 2008a; 2009b; Summerton et al. 2008).

(31) ***Adopting Healthier Lifestyles: Reducing the incidence of leftover drugs may in some instances also serve to reduce the entry of APIs to sewers via excretion and bathing***. A potentially significant collateral benefit from minimizing the need for disposing of drugs has yet to be recognized. Although minimizing leftovers by increasing patient compliance may increase the quantities of those APIs excreted unchanged or discharged to sewers by way of bathing, minimizing leftovers resulting from unnecessary or imprudent prescribing (e.g., wrong medication) will reduce API excretion. Of the numerous facets of medical care that can be modified to reduce the incidence of drug accumulation and subsequent need for disposal, many would entail modification of dosage regimes, generally resulting in lower amounts over the course of treatment. *Lower overall dosing (e.g., via evidence-based prescribing and personalized prescribing) will necessarily result in lower excretion. By taking actions to reduce the need for drug disposal, overall drug usage can decrease.* Residues entering sewage from both disposal and excretion could thereby be reduced simultaneously. *The control of usage is perhaps more capable of reducing overall entry of APIs to the environment, as it can eliminate the need for disposal plus minimize the residues released by excretion and bathing*. Usage control is much more complex than disposal control as it entails the involvement of the entire healthcare community, including healthcare insurers.

(32) ***Counter to current perception, excretion of APIs can be reduced – without jeopardizing the quality of healthcare.*** A critical misconception is that control of API entry to the environment must focus on better control of disposal because excretion is not a factor that can be controlled. As already pointed out in the prior item (above), the wherewithal already exists for partly controlling the quantities of APIs excreted. The suggestion made immediately above regarding optimal, lower doses is clearly a major way this can be accomplished. Other ways include personalized prescribing (using pharmacogenomics) to avoid the prescribing of APIs to those who are poor responders - or to perhaps reduce the dose for those who are poor metabolizers (Daughton and Ruhoy 2010). But another little-recognized approach for reducing excretion would be factoring pharmacokinetics into the drug selection process before prescribing. For example, within a given therapeutic class, there may be certain APIs whose metabolism results in much less excretion of unchanged APIs than others.

(33) ***Several trends hold potential for exacerbating the need for prudent drug disposal***. In its most recent drug-usage survey "U.S. Prescription Drug Data for 2007–2008," the CDC reports a continuing upward trend over the last 10 years in the numbers of prescriptions issued in the month preceding the survey (Gu et al. 2010). Usage rates increased across all ages, with rates of polypharmacy (5 or more drugs) particularly increasing for those of age 60 or greater. Those with more than one prescription drug in

the prior month increased by 10% over the last 10 years, those with more than one drug increased by 20%, and those with five or more increased by 70%. One-half of the population used prescription drugs - including 20% of children and 90% of those older than 60.

Several trends are resulting in a greater variety and larger quantities of pharmaceuticals being used within the home. The trend that has attracted the most attention is the continuing rise in prescription drug abuse, especially opiate pain killers. The continuing escalation in abuse of prescription drugs is reflected by the attention devoted by the popular press, where new terms have emerged to distinguish “America’s new drug crisis” from previous trends in drug abuse (dominated by illicit drugs) – terms such as “addiction by prescription” and “pharmageddon” (e.g., Kluger 2010).

But other, less-recognized trends will also play key roles. One is earlier discharge from hospitals and continuation of care at home. Another is the increasing provision of hospice care at home. These tend to increase the quantities of leftover drugs needing disposal by the consumer. Another is the commercialization of ever-more potent drugs (referred to as "highly potent active pharmaceutical ingredients" HPAPIs) and more routine and widespread use of synthetic opioids, genotoxics, and cytotoxics (such as chemotherapeutics), with uses expanding not just in homes, but also in veterinary practices; these drugs pose unique challenges with respect to physical handling (by those wishing to dispose of them or those who must dispose of resulting medical waste), as well as the critical importance of preventing access to them in households, especially for those drugs having single-dose fatality potential. Drug usage in general is forecast to continue increasing; one driver in Asia is reduction in prices to produce larger sales volumes (Matsuyama 2010).

Advances in pharmacogenomics have the potential to both: (i) greatly increase the numbers of low-usage drugs (those specifically tailored to narrowly defined patient populations, serving to vastly increase the number of therapeutic niches), and (ii) increase the numbers of high-usage (“block-buster”) drugs - by addressing therapeutic targets of minimal genetic variability across the population to yield drugs of extremely broad tolerability. By increasing the efficiency of drug discovery (minimizing failures), the resulting reduced costs will allow more discovery. So the application of pharmacogenomics could accelerate the development of new drug entities or expanded use of existing drugs.

Home storage and stockpiling of medications may also increase because of the increasing interest in self-diagnosis and self-medication (due to greater - but not necessarily better - availability of information, such as via the Internet) and the more ready access to medications. One trend that is increasing the incidence of self-medication or self-administration (and increased purchase of medications) is prescription-OTC switches. A long-ongoing debate surrounds the switching of certain drugs from prescription only to OTC. The process by which prescription drugs are switched to nonprescription, over-the-counter (OTC) status is known as the "Rx-to-OTC switch." In the past, switching has occurred for drugs used for short-term sporadic treatment, such as certain antihistamines.

The debate becomes more complicated with medications designed for long-term maintenance. The statins serve as an excellent example of efforts from industry to gain FDA approval of Rx-OTC switches (Tinetti 2008). The debate has centered on whether consumers can properly self-manage long-term conditions. Regardless of the many factors that enter into this debate, it is very clear that switches will undoubtedly promote increased purchasing and inevitably the accumulation of yet more unused drugs. Since the consumer has no boundaries on decisions to self-medicate, Rx-to-OTC switches greatly expand the spectrum of conditions for which treatment can be attempted, further escalating drug use. Given the prescription-only APIs or dosage strengths that were available in the US 25 years ago, now over 700 formulated products incorporating this same APIs are available OTC. A listing of the nearly 100 APIs that have undergone the Rx-to-OTC switch since 1976 is available from CHPA (2009).

Designing pollution prevention measures for OTC drugs is much more difficult than for prescription-only medicines, as control measures cannot be implemented at the level of physicians and pharmacists. Moreover, while retailers of OTC medications could be seen as having a major role to play in changing consumer behavior regarding excessive purchase (e.g., avoiding quantities too large to consume before expiration), their roles as for-profit businesses could at least give the appearance of a conflict.

Storage in the home also exacerbates self-medication, creating a reinforcing feedback loop that encourages more stockpiling. The incidence of leftover medications becomes a factor that serves to amplify its own magnitude. Leftover medications tend to result in yet more leftovers. The greater the accumulation, the harder it is to keep track of them, leading to ever-greater difficulty in maintaining compliance. Leftover medications become an ever-escalating problem, especially as the incidence of polypharmacy grows. Polypharmacy at one time was driven primarily by the aging population, but it is also becoming more prevalent in younger populations, as the incidence escalates for chronic diseases, especially obesity and diabetes (becoming referred to as “diabesity”).

A particular aspect of hoarding leftovers and its encouragement of self-medication is the inappropriate use of antibiotics and its propensity to select for antimicrobial resistance. The lack of appropriate and fast drug disposal could therefore be a potential contributor in drug resistance. One self-medication study focused on the use of antimicrobials in Europe (Grigoryan et al. 2006). The authors estimated the incidence of self-medication using antimicrobials in 19 European countries to be 1 to 210 per 1,000 population, a very high rate. Drug storage was a good predictor of future self-medication. The study of Grigoryan et al. (2006) also hinted toward a possible environmental justice component: "Substantial variation in the prevalence rates of antimicrobial drug self-medication among the European regions suggests that cultural ... and socioeconomic factors play a role, as do disparities in health care systems such as reimbursement policies, access to health care, and drug dispensing policies."

(34) ***Manufacturer promotions such as Direct-to-Consumer (DTC) advertising and drug sampling increase the incidence of leftovers***. The negative influence of drug promotions as a factor in the accumulation of leftover drugs could be

counteracted with a variety of measures largely targeted at reducing the use of drug sampling (provision of free samples to physicians). Formal “counter-detailing” programs exist for educating physicians on evidence-based prescribing and the negatives of free samples. Many of the negative attributes of free samples could be reduced if physicians employed vouchers, where patients could then obtain the free samples from the pharmacy. This would greatly reduce the influence of free samples on immediate drug waste (by avoiding expiration within the physician’s office), diversion, and leftovers (as a portion of patients are known to accept free samples with no intention of ever using them, and would then choose to not have the voucher filled).

(35) ***Certain trends such as large-scale drug diversion may be exacerbating the need for drug disposal***. Illegal activities involving prescription drugs, such as drug diversion and theft, have previously unrecognized connections with the drug disposal issue. Large-scale diversion of certain drugs due solely to theft (especially hydrocodone, oxycodone, morphine, methadone, hydromorphone, meperidine, and fentanyl) (see: Inciardi et al. 2007) probably increases the need for greater manufacturing to replace these lost inventories and to meet legitimate prescribing needs. This serves not only to amplify the residues of these APIs ending up in the environment via excretion, but probably also amplifies the need for disposal - as leftovers and wastage probably occur for both the diverted supplies and for the replacements. During 2000 through 2003, in just 22 eastern states, roughly 28 million doses of these drugs were reported stolen or "lost"; also see Solomon (2010). Perhaps for no other consumer product does theft make such a significant contribution to environmental pollution. Since drug counterfeiting sometimes relies on diverted pharmaceuticals, it too may be directly connected with the need for greater disposal.

MESSAGING & COMMUNICATION

(36) ***Current science can only justify a focus on drug disposal on the basis of the collateral benefits for healthcare and protecting human safety - not for protecting the environment***. On the basis of available science, the only demonstrated benefits from devising alternative drug disposal systems (e.g., to reduce or eliminate flushing into sewers) that can be currently justified are collateral benefits involving healthcare (e.g., improvements in therapeutic outcomes and reduced healthcare costs from measures designed to optimize the use of medications). The design and implementation of programs for controlling leftover medications (by "proper" disposal or by pollution prevention measures designed to minimize or eliminate leftovers) can currently be based only on hypothetical risks. No published data could be found to support the four major drivers that have been highlighted for the need for prudent drug disposal, namely, the need to reduce: (1) unintentional poisonings, (2) diversion and abuse, (3) inappropriate donations, and (4) residues of APIs in the aquatic ambient environment. It is simply not yet known whether better disposal of leftover drugs would have any impact in reducing the loadings of APIs in the environment. The major driver behind development of alternative drug disposal schemes is therefore rooted in benefits to the healthcare system rather than for the environment. While benefits to healthcare would certainly constitute a notable outcome, they would require substantial progress in pollution prevention rather than in handling of the drug waste itself. Focusing limited

resources on controlling or optimizing the myriad processes upstream of drug waste therefore holds potential not just for what is currently only a hypothesized possibility of reducing adverse impacts on the environment, but more importantly for the more probable improvements that could result in many of the facets of healthcare and human safety.

(37) ***Possible unexpected paradox: Drug take-back events may potentially worsen the drug disposal problem, as well as diversion and poisonings, by encouraging stockpiling*.** The approach used in nearly all collections activities is physical transport by the consumer to the drop-off site. This approach incurs added costs from transportation and consumer time, and requires planning ahead. Some consumers are unable to conveniently travel and many locales do not have access to collection sites. Most importantly, however, the use of episodic take-back events may be inadvertently encouraging and perpetuating one of the major consumer behaviors long-sought for elimination by drug control programs. Episodic take-backs can facilitate or force the consumer to amass and store leftover medications - a practice that imposes the same risks for diversion and unintended poisonings as does hoarding. A continual returns program, such as mail-backs, can avoid this shortcoming, as shown by the Maine pilot program (Kaye et al. 2010).

Public outreach has been a major approach for attempting to correct several of the problems surrounding drug disposal. One of the major objectives of the ONDCP, for example, has been to draw a tight connection between drug stocks in the home with an increased incidence of both drug abuse and accidental poisonings. These themes have been repeated by most of those involved with the drug disposal issue. Although this approach might seem to be one having clear and positive outcomes, this is an assumption that has little corroborative evidence. Other than questions as to whether more rapid disposal will impact these endpoints, a question and concern that emerges from this approach is whether this type of public relations campaign may actually exacerbate the problem. By advertising that drugs stored at home are being diverted for recreational purposes, could this be making diversion and drug experimentation worse? This would be analogous to the concerns that the reporting of drug abuse by the media may be an additional cause of drug poisonings rather than just reflecting the news (Dasgupta et al. 2009). This is an important question - one that deserves investigation in case the current approach to public communication unexpectedly proves counterproductive.

Formal drug disposal programs need to be accompanied with public messages explaining that the generation of leftover drugs is not necessarily an acceptable practice. But by having the public focus on "proper disposal," a major existing risk could be greatly exacerbated depending on how convenient the disposal options are. Some consumers might be tempted to store their unwanted drugs until the stockpiled quantity is sufficiently large that it warrants transport to a disposal location. Storage in the home of larger quantities of more types of drugs simply increases the possibility of access by those who could be involved with diversion or unintended poisoning.

Perhaps the most ironic aspect of programs designed for prudent disposal of medications is that formal disposal programs might unwittingly encourage the replacement of these medications with new stocks and thereby generate yet more waste - perpetuating the cycle of excessive, repeated purchase and disposal. By facilitating easy, "cost-free" disposal of drugs with formal take-back programs, consumers may be inadvertently encouraged to not hesitate in buying additional large quantities (to achieve false economies of lower unit-dose pricing), only to again find themselves unable to fully consume them before expiration. Disposal would then be followed by repurchasing new supplies. Instead, a larger more holistic message needs to be conveyed to the consumer - one where leftover drugs are an indirect measure of wasted resources, lost opportunities to achieve desired therapeutic outcomes, poor purchasing decisions, and further burden for the environment. Indeed this problem has been alluded to by others: “Easing regulation of waste disposal [namely, with regard to modifying the Universal Waste Rule] decreases institutional motivation for waste reduction and pollution prevention” (Tucker 2009).

The public message needs to be directed at points further up the chain of events that lead to the acquisition of medications - not a focus on the availability of disposal programs. Better public awareness of the larger issue (the actions, activities, and behaviors that lead to the need for disposal) could reduce unrealistic expectations, imprudent use (especially self-medication), and stockpiling.

The psychology of drug returns indicates that another factor may be at play. A UK study of consumer drugs returned to pharmacies discovered that many patients were "shocked" to learn that their returned drugs were going to be destroyed. They had falsely believed that their unused medications were going to be redistributed to others who were in need. It could be important to determine if this is a common perception in the US, as it might alter people's decisions to fill unnecessary scripts or those they had no intention of ever using (knowing in advance that if they did not actually use the medication, it could not be made available to someone else) (Bradley 2009).

(38) ***Public outreach efforts designed to promote prudent disposal should try to ensure that certain, select groups are reached***. Evidence exists that a small portion of consumers overall are responsible for a disproportionately large portion of drugs that eventually become leftovers. A study by Ekedahl (2006) reported that 25% of all medicines collected in a Swedish returns program came from just 3% of those making the returns. If this behavior translates to other countries, then this small, select group of consumers needs to be influenced by public outreach programs to ensure high rates of prudent disposal.

(39) ***Public outreach efforts and mechanisms for prudent drug disposal should try to accommodate consumers with unusual needs*.** Unforeseen circumstances often add complexity to design of prudent and useful disposal programs. Given the growing incidence of drug abuse and addiction, one particular source of stockpiled drugs comprises the caches accumulated by addicts who have begun addiction recovery therapy. These individuals commonly have large stockpiles of drugs - primarily

comprising controlled substances. Wishing to avoid being discovered by law enforcement, they cannot discard these substances into the trash or hand over to law enforcement. The lack of an acceptable means of disposal may result in these drugs remaining stockpiled indefinitely (increasing the risks of diversion and unintended poisonings) or flushed down the toilet (Lessenger and Feinberg 2008).

(40) ***Unknowns surrounding the connection of expired drugs with toxicity***. One of the major drivers and justifications for consumers to clear their supplies of medications is the purported hazard associated with expired drugs. Despite the considerable research and data developed for drug registration on API stability and expiry, the evidence that expired drugs pose toxicological concerns is extremely thin. At worst, expired medications simply lose potency and therefore are not as effective (albeit this can obviously cause concerns for achieving therapeutically effective doses). As a driver for take-backs, the public message regarding expiry might instead be based on potency, not on toxicity. But moreover, the extensive shelf-life research program initiated by the Department of Defense, and research by independent investigators, has demonstrated that many medications when stored under controlled conditions (but generally not achievable by the consumer) can remain effective for years past expiration. This points to the possibility of improving the accuracy of declared expiration dates, with the potential to reduce the need for disposal.

(41) ***Non-compliance can be targeted as a means to better involve the patient in effecting change***. Consumers (and many in the healthcare industry) do not fully understand the intimate inter-connections between non-compliance and a spectrum of other adverse outcomes, including: sub-optimal therapeutic outcomes, increased healthcare costs (not just from wasted medications, but also from the increased need for future treatment because of incomplete or insufficient current treatment), and possible environmental impacts. With communication targeted at the patient (and physician) showing that all of these factors are intimately linked, more progress could possibly be made in reducing drug usage (and therefore excretion) as well as the generation of leftovers. This could be achieved by a combination of patient education and by the use of innovative labeling. Drug usage could be optimized if the patient better understood up front - before a script were issued and filled - that restricting medications to those known to be effective and by taking their medications as prescribed could reduce future healthcare costs, better optimize therapeutic outcomes, and protect the environment. With a better appreciation regarding the many benefits for improved compliance and active collaboration with the physician (such as alerting the physician when directions are unclear or when adverse effects occur), the patient could become more motivated to play an active and productive role in minimizing the impact on the environment by APIs.

(42) ***Centralized coordination needed for all issues related to stewardship and disposal - minimizing waste of resources that leads to duplication of effort, rediscovery, and reinvention***. While the drug disposal issue only emerged as a topic of discussion in the US roughly 5 years ago, very substantial investments in time, money, and effort have been devoted to the topic by a broad array of public and private organizations and agencies. Because of the sheer number of participants and

stakeholders, there has been considerable duplication of effort, much of it simply amounting to rediscovery or reinvention - and much leading to dead ends. The vast majority of all publications that deal with some aspect of drug disposal simply restate what prior articles have already stated - especially with regard to guidance for disposal. This promotes group think and its attendant liability of preventing truly effective solutions. Moreover, this points to the need for a lead agency (or at least a national clearinghouse or institute) responsible for setting the agenda and coordinating efforts along the many fronts of inquiry surrounding the expansive drug disposal issue.

There are many other findings, some of which are dispersed throughout this document. Others can be derived by reading the supporting documents that compose the foundation for this project. The overall topic of drug disposal is so deceptively complex - involving many professions, spanning numerous fields of study, and involving countless processes - that it cannot be covered in a truly comprehensive manner in a single report. This reiterates the importance of the background documents and the published literature captured in the electronic database (DDS) described later in this report.

The refractory problem of drug disposal is remarkable in that a solution that balances human health and safety while also protecting the environment will require a truly transdisciplinary collaboration. A holistic solution will involve the concerted efforts of numerous private, public, and government entities. It must be based on science to have maximum impact and expend public resources effectively.

Despite the decades of debate and discussion surrounding drug disposal, surprisingly no single comprehensive resource exists that examines and distills what is known (and what further needs to be known) and provides a synoptic overview of this multi-faceted topic. While this report too is not comprehensive, it strives to provide the most in-depth balanced view to date.

SCOPE AND OBJECTIVES

More than any other aspect of the overall topic of pharmaceuticals as environmental contaminants, disposal of "leftover" consumer drugs has consistently attracted the most attention from the public, the media, local and state regulators, and the healthcare community. Leftover drugs are those that have expired or are no longer needed, wanted, or desired (because they are no longer effectual or have undesired side effects). For all of those who have tackled the issue of drug disposal over the years, it has always seemed to be one that could be easily solved. With appearances aside, the singular feature of drug disposal that quickly emerges from all attempts at solutions is that it is a surprisingly and deceivingly complex, convoluted, and frustrating problem - one that continually encounters myriad obstacles and pitfalls that thwart all attempts at effective and efficient solutions.

If the focus of this report were simply on how to best dispose of leftover drugs, the discussion would quickly distill down to a narrow focus on regulatory obstacles and on local and state legislation that attempts to enable various means of collecting leftover medications from the public (so-called "take-back" or "returns" programs), the design considerations and logistics involved with implementing take backs, and the limited published literature on leftover drugs (such as data collected from take-back programs or from in-home inventories). But this would not address the real issue - one that has far greater potential for achieving broad and sweeping outcomes. The real issue is one of stewardship and sustainability spanning the complete lifecycle of pharmaceuticals. This vastly expands the scope and complexity of the issue.

Therefore, this report's main objectives are to: (i) summarize what is currently known regarding whether the disposal of consumer medications contributes significant fractions of environmental residues of APIs (a finding required to justify and design consumer drug take-back programs), (ii) reveal the numerous factors that dictate why and whether medications eventually require disposal, (iii) show how these factors can be altered to reduce the accumulation of unused drugs and their consequent need for disposal, (iv) explain how efforts to control the actions, activities, and behaviors that contribute to the need for drug disposal could serve to catalyze many improvements in the nation's healthcare system, and (v) foster advancement of a new concept (pharmEcovigilance) regarding environmental stewardship of medications - a concept that could help protect ecological and human health as well as reduce the incidence of poisonings caused by diversion of medications awaiting disposal. The report provides an integrated overview of the key elements and findings, along with recommendations.

Some of the key questions addressed in the documents prepared for this report include:

- where do leftover drugs accumulate in society?
- what causes their accumulation?
- what are the current routes of their disposal?
- what portion of drug residues in the environment originate from disposal?
- what are the risks of unwanted drugs for humans, domestic animals, and wildlife?
- how can the accumulation of excess medications by consumers be minimized or eliminated?
- how can these unwanted drugs be best disposed?
- are there potential benefits beyond reduced environmental impact?

A major outcome sought by the final report is to provide a science-based framework for discussing, justifying, and designing a nationwide approach for dealing with the accumulation and disposal of unwanted medications. The objective is to minimize exposure of humans and wildlife to ambient levels of APIs while at the same time ensure collateral improvements in our system of health care. The problem needs to be examined from two perspectives: not just down-stream pollution control, involving the most efficient and prudent approaches for disposal, but more importantly up-stream pollution prevention, aimed at reducing or minimizing the need for disposal.

Long overlooked in the debate surrounding consumer drug disposal is the larger imperative to reduce or eliminate the need for disposal in the first place - - by a wide spectrum of approaches targeted at pollution prevention. Drugs accumulate unused for a wide variety of reasons, each of which presents opportunities for reducing the need for disposal (Ruhoy and Daughton 2008).

These reasons range from patient non-compliance (which itself has a plethora of causes), inefficient oversight of the prescribing process by physicians, imprudent dispensing practices by the retail pharmacy and insurance industry, and wasteful packaging by manufacturers. A wide array of causes for accumulation and subsequent disposal are summarized by Ruhoy and Daughton (2008); many of these are summarized in Figure 3 of that article. Another significant aspect of medication accumulation is the broad spectrum of locations in society where medications are stored and where they eventually can accumulate unused (for example, upon expiration), ranging from zoos and all public buildings (e.g., first aid kits), to schools and cruise ships; many of these are summarized in Figure 4 of Ruhoy and Daughton (2008). The numbers and types of places go far beyond the traditional view of the home medicine cabinet.

Perhaps the most important point to understand with respect to the many routes leading to drug accumulation and disposal is that these represent the most productive avenues for pursuing pollution prevention. To minimize or eliminate the occurrence of leftover drugs represents a much more efficient way to deal with the many problems faced by the need for drug disposal. Of most significance, preventing the need for disposal in the first place not only eliminates the resources required for environmentally sound drug disposal programs, perhaps more importantly it serves to conserve and make more efficient use of medications for their intended purposes (through prudent, evidence-based prescribing), thereby reducing healthcare costs and improving healthcare outcomes. In the process, reducing drug usage also reduces the first two routes of entry to the environment - - excretion and bathing (Daughton and Ruhoy 2008b).

With this said, however, the focus in the U.S. has remained on how to best dispose of drugs with minimal environmental impact, rather than on the need to generate less medication waste. To date, this has been done in the US with relatively inefficient one-time community collection events or on-going local programs that vary in their scope and design across geographic locales. The most visible of consumer-based collection approaches are known as "take-backs" or "returns," but other means also exist, including mail-backs. A disparate patchwork of these collection programs exists sporadically across the U.S. The EPA has been evaluating a pilot demonstration of one approach that may prove to be more sustainable - one that could be implemented nationwide - designed to make use of the US Postal Service (Gressitt 2005; University of Maine 2008). A second pilot program involved the return of consumer medications through a pharmaceutical reverse distributor via UPS (Hendrickson 2010). While consumer take-back programs are a relatively new concept in the U.S., they have been in place in Europe for over 30 years. Three of the earliest publications dealing with formal drug take-backs are Bradley and Williams (1975), Harris et al. (1979), and Sixsmith and Smail (1978).

To shift the emphasis of the discussion away from disposal and toward the many aspects of stewardship and pollution prevention will require an active dialog between experts from the various healthcare communities and from the environmental science community. Bridging these two sectors has never been done. To date, there have been extraordinarily few publications in the medical or healthcare literature that discuss the fact that medications have afterlives as environmental pollutants (e.g., Daughton 2002; Daughton and Ruhoy 2008a; Zuccato et al. 2000). An approach that integrates the monitoring of adverse events in medicated humans as well as adverse events in the environment has been termed pharmEcovigilance (Daughton and

Ruhoy 2008b). Its main focus is on identifying and reducing those sources of APIs that contribute to unintended human and ecological exposure.

A pharmEcovigilance program would focus on the numerous points along the expansive network spanning from manufacturers to patients - - where medications are designed, packaged, prescribed, dispensed, and consumed, and where numerous processes and procedures could be redesigned or altered to ensure optimal therapeutic outcomes from minimized drug use. The ultimate objective and measure of success would be the degree to which medications are fully consumed (reducing leftovers) while maintaining or improving therapeutic outcomes. This could be achieved by redesigning a system that can get the right medication to the patient at the optimal dosage and dosing time, and total quantity appropriate for the situation - and to choose the most efficacious medication having the smallest environmental footprint and affordable cost (Daughton 2009). This must be coupled with a system that provides rapid feedback on therapeutic success, adverse events, and non-compliance. Such a program could lead to a more efficient, optimized healthcare system, improved therapeutic outcomes and cost. Reduced environmental impact would then become a natural outcome of better healthcare. While all of this remains hypothetical, as sufficient data and knowledge to accomplish it are lacking, it emphasizes that an unbalanced focus on drug disposal alone could miss much greater opportunities.

PharmEcovigilance would emphasize that human and ecological health are intimately connected. It would seek to optimize the design of the life cycle of drug manufacturing, sales/distribution, and usage by ensuring: (1) prescribing the most effective medications in efficacious minimal doses individualized for each patient, (2) dispensing in quantities and for durations that ensure patient compliance (full consumption), and (3) minimizing/eliminating the generation of leftover medications - so the need for disposal is avoided. Its major objectives would be to: (1) minimize impacts on the environment from APIs as pollutants, (2) minimize exposure of humans via consumption of APIs "recycled" from the environment (trace residues in drinking waters and foods), and (3) minimize hazards posed to safety and health from accidental exposure or diversion or scavenging of unused medications by humans, pets, and wildlife (Daughton 2008; Daughton and Ruhoy 2008b).

One tenet of pharmEcovigilance is whether an imperative exists to now begin treating human and ecological health as one and the same. The historical disconnect between human health and ecological integrity still persists. Social, scientific, engineering, and regulatory systems traditionally divide and separate what is really one integral system. The health of humans and ecological integrity and sustainability are intimately intertwined. This becomes evident when the processes involved with drug disposal are examined in detail.

The many actions that could be considered for prudently reducing drug use (and thereby reduce the need for disposal) have been summarized in several publications: (Daughton 2003a; b; Daughton and Ruhoy 2008b; Ruhoy and Daughton 2008). The prudent reduction in overall medication usage could minimize the need for disposal. To reiterate, in contrast to improving the drug disposal process, pollution prevention actions might afford the potential for significant collateral benefits in reducing healthcare costs and improving therapeutic outcomes, as well as reducing entry of APIs to the environment via excretion and bathing. The major emphasis to

date, however, has been on improving approaches for drug disposal. The most important thing to keep in mind with respect to disposal is the many unknowns regarding its benefits and sustainability. These unknowns will serve as the focus of much of the discussion that follows.

PROJECT COMPONENTS

Pursuit of these objectives resulted in a comprehensive body of work from EPA's ORD comprising a series of seminal publications in the peer-reviewed archival literature, invited presentations at scientific conferences, and construction of the world's most complete electronic database of all forms of published literature that are relevant to the many aspects of leftover drugs, drug disposal, and environmental stewardship and pollution prevention. These products serve as the foundation for this report. The report serves to synthesize the data, knowledge, and insights from these publications and those captured in the contents of the literature database. Note, however, that only a small portion of the references captured in the DDS bibliographic database are cited in this report.

The main products in addition to the bibliographic database are 7 peer-reviewed journal articles, 5 book chapters, over 20 invited presentations at scientific and programmatic conferences, a doctoral dissertation, roughly 10 posters and technical illustrations, and various outreach activities (particularly, numerous interviews with the mass media, addressing inquiries from the public, State Attorneys General, Congressional staff, GAO, and EPA program offices). The major products published from this project are listed below. Digital reprints can be obtained from daughton.christian@epa.gov, but versions of most of these documents can be directly accessed and downloaded from:

"Drug Disposal & Stewardship: Ramifications for the Environment and Human Health," U.S. Environmental Protection Agency, Las Vegas, Nevada (web page maintained by CG Daughton); available: http://www.epa.gov/ppcp/projects/disposal.html

Journal Articles:

Daughton CG and Ruhoy IS. "PharmEcovigilance: prescribing to protect the planet and improve healthcare," invited article for *Expert Review of Clinical Pharmacology*, targeted for March 2011 (in preparation).

Daughton CG and Ruhoy IS. "Environmental Footprint of Pharmaceuticals: The Significance of Factors Beyond Direct Excretion to Sewers," *Environmental Toxicology & Chemistry* (special issue: Pharmaceuticals and Personal Care Products in the Environment) **2009**, 28(12):2495-2521; doi:10.1897/08-382.1; available: http://www3.interscience.wiley.com/cgi-bin/fulltext/123234136/PDFSTART.

Glassmeyer ST, Hinchey EK, Boehme SE, Daughton CG, Ruhoy IS, Conerly O, Daniels RL, Lauer L, McCarthy M, Nettesheim TG, Sykes K, and Thompson VG. "Disposal Practices for Unwanted Residential Medications in the United States," *Environment International*, **2009**, 35(3): 566-572; doi:10.1016/j.envint.2008.10.007.

Daughton CG and Ruhoy IS "The Afterlife of Drugs and the Role of PharmEcovigilance," *Drug Safety*, **2008**, 31(12):1069-1082; doi: 10.2165/0002018-200831120-00004.

Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environment International*, **2008**, 34(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available: http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf.

Ruhoy IS and Daughton CG "Types and Quantities of Leftover Drugs Entering the Environment via Disposal to Sewage - Revealed by Coroner Records," *Science of the Total Environment*, **2007**, 388(1-3):137-148; doi 10.1016/j.scitotenv.2007.08.013; available: http://www.epa.gov/nerlesd1/bios/daughton/SOTE2007.pdf.

Daughton CG "Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health. I. Rationale for and Avenues toward a Green Pharmacy," *Environmental Health Perspectives*, **2003**, 111(5):757-774; doi: 10.1289/ehp.5947; available: http://www.epa.gov/nerlesd1/bios/daughton/green1.pdf.

Daughton CG "Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health. II. Drug Disposal, Waste Reduction, and Future Direction," *Environmental Health Perspectives*, **2003**, 111(5):775-785; doi: 10.1289/ehp.5948; available: http://www.epa.gov/nerlesd1/bios/daughton/green2.pdf.

Book Chapters:

Daughton CG and Ruhoy IS. "Pharmaceuticals in the Environment - Why Should We Care?" In: Pharmaceuticals in the Environment: Current Knowledge and Need Assessment to Reduce Presence and Impact, B. Roig (Ed.), IWA Publishing, London, UK, Foreword, pages xiii-xvii, **2010** ISBN: 9781843393146
http://www.epa.gov/esd/bios/daughton/IWA -2010.pdf;
http://www.iwapublishing.com/template.cfm?name=isbn9781843393146

Daughton CG and Ruhoy IS. "Reducing the Ecological Footprint of Pharmaceutical Usage: Linkages between Healthcare Practices and the Environment," In: Green and Sustainable Pharmacy, Klaus Kümmerer and Maximilian Hempel (Eds.), Springer, Chapter 6, **2010**, pages 77-102; ISBN: 978-3-642-05198-2; http://www.springer.com/environment/environmental+management/book/978-3-642-05198-2

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**; ISBN: 2184-01; available: http://www.epa.gov/nerlesd1/bios/daughton/Pharmaceuticals-Sustainability-2009.pdf.

Daughton CG and Ruhoy IS "PharmEcovigilance: Aligning Pharmacovigilance with Environmental Protection," In: An Introduction to Environmental Pharmacology, SZ Rahman, M Shahid, and V Gupta (Eds.), Ibn Sina Academy, Aligarh, India; **2008**, Chapter 1 (Introductory Overview), pp 21-34; ISBN # 978-81-906070-5-6; available: http://www.epa.gov/nerlesd1/bios/daughton/IntroEnvironPharmacol-Chapter1-2008.pdf.

Daughton CG and Ruhoy IS "Accumulation and disposal of leftover medications: A key aspect of pharmEcovigilance," In: An Introduction to Environmental Pharmacology, SZ Rahman, M Shahid, and V Gupta (Eds.), Ibn Sina Academy, Aligarh, India; **2008**, Chapter 5, pp 101-107; ISBN # 978-81-906070-5-6; available: http://www.epa.gov/nerlesd1/bios/daughton/IntroEnvironPharmacol-Chapter5-2008.pdf.

Posters & Illustrations:

Daughton CG "Illicit Drugs and the Environment," [illustration published in: Daughton CG "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology," *Reviews of Environmental Contamination and Toxicology*, in press, March 2011)], US EPA, Las Vegas, Nevada, 7 December 2009 (rev 17 June 2010).

Daughton CG and Ruhoy IS. "PharmEcokinetics of APIs [illustration published in: Daughton, C.G. and Ruhoy IS "Environmental Footprint of Pharmaceuticals - The Significance of Factors Beyond Direct Excretion to Sewers," *Environmental Toxicology & Chemistry*, **2009**, 28(12):2495-2521; doi:10.1897/08-382.1]," US EPA, Las Vegas, NV, 7 June 2008.

Daughton CG. "Role of PharmEcovigilance: Minimizing Human & Ecological Impacts [illustration published in: Daughton CG and Ruhoy IS "The Afterlife of Drugs and the Role of PharmEcovigilance," *Drug Safety*, **2008**, 31(12):1069-1082]," US EPA, Las Vegas, NV, 16 April 2009.

Daughton CG and Ruhoy IS. "PharmEcovigilance & Stewardship: Reducing Human and Ecological Exposure from Pharmaceutical Residues," illustrated poster prepared for the "Environmental Sciences Division Peer Review," 14 May 2009, National Exposure Research Laboratory, Office of Research and Development, US EPA, Las Vegas, NV, Session 5: Water Quality – Stressor/Receptor Characterization, poster #SRC-3; available: http://www.epa.gov/esd/chemistry/images/pharmEcoviginlance_stewardship.pdf.

Daughton CG. "Unintentional, Unanticipated Exposure to Drugs [illustration published in: Daughton CG and Ruhoy IS "The Afterlife of Drugs and the Role of PharmEcovigilance," *Drug Safety*, **2008**, 31(12):1069-1082]," illustration, US EPA, Las Vegas, NV, 8 December 2007 (rev 4 June 2008) 2007.

Daughton CG. "Accumulation and Disposal of Pharmaceuticals [illustration published in: Ruhoy IS and Daughton, C.G. "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, **2008**, 34(8):1157-1169]," US EPA, Las Vegas, NV, 10 May 2008.

Daughton CG. "Factors Influencing Drug Consumption [illustration published in: Ruhoy IS and Daughton, C.G. "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, **2008**, 34(8):1157-1169]," illustration, US EPA, Las Vegas, NV, 8 December 2007 (rev 28 April 2008).

Daughton CG. "The Environmental Life Cycle of Pharmaceuticals [illustration published in: Daughton, C.G. "Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure," In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, San Diego: Academic Press; **2008**, pp. 66-102]," US EPA, Las Vegas, NV, December 2006**;** available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf.

Daughton CG. "PharmEcovigilance and Environmental Risk [published in: Daughton CG and Ruhoy IS "PharmEcovigilance: Aligning Pharmacovigilance with Environmental Protection," In: An Introduction to Environmental Pharmacology, Ed. SZ Rahman, M Shahid, and V Gupta, Ibn Sina Academy, Aligarh, India; **2008**, Chapter 1, pp 21-34]," US EPA, Las Vegas, NV, 4 November 2007.

Ruhoy IS and Daughton CG "Pharmaceutical Disposal and the Environment," U.S. EPA, Las Vegas, NV; illustrated poster, December 2007, NERL-LV-ESD-07-132; available: http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-2.pdf.

Ruhoy IS and Daughton CG "Disposal as a Source of Pharmaceuticals in the Environment," U.S. EPA, Las Vegas, NV; illustrated poster, December 2007; NERL-LV-ESD-07-129; available: http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-1.pdf.

Other:

Daughton CG "Drug Usage and Disposal: Overview of Environmental Stewardship and Pollution Prevention (with an emphasis on activities in the Federal Government)," US EPA, Office of Research and Development, Environmental Sciences Division, Las Vegas, Nevada, 23 pp, 15 October 2008; prepared for: Research Triangle Environmental Health Collaborative - an Environmental Health Summit, "Pharmaceuticals in Water: What We Know, Don't Know, and Should Do," 10-11 November 2008, North Carolina Biotechnology Center, Research Triangle Park, North Carolina; available: http://environmentalhealthcollaborative.org/summit/presentations-and-materials/; http://environmentalhealthcollaborative.org/images/ChristianDaughtonAbstract.pdf.

Ruhoy IS and Daughton CG. "Drug Disposal and Environmental Stewardship," invited presentation for teleconference call on Drug Disposal for area agencies on aging in Maryland, organized by EPA's Aging Initiative and the Office of Water, 22 June 2010; available: http://www.epa.gov/aging/resources/ddes/index.html.

Ruhoy, Ilene Sue "Examining Unused Pharmaceuticals in the Environment," Ph.D. Dissertation, University of Nevada, Las Vegas, Dept. Environmental Studies; August 2008, publication number 3352183; ISBN 9781109091083; 153 pp; accessible: http://gradworks.umi.com/33/52/3352183.html.

Daughton CG "Environmental Stewardship of Pharmaceuticals: The Green Pharmacy," In: Proceedings of the 3rd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, National Ground Water Association, 19-21 March 2003, Minneapolis, MN, p. 5-14; available: http://www.epa.gov/nerlesd1/bios/daughton/ngwa2003.pdf.

Literature Database:

A major problem that pervades the field of pharmaceuticals and personal care products (PPCPs) is that the published literature tends to languish unused (Daughton 2009). Little of it is ever read - leading to much reinvention, duplication, and failure to capitalize on existing knowledge. Since the field is now so large, it is no longer possible to summarize in a useful manner the published literature surrounding its many facets, including that of drug disposal. This was one of the major reasons behind assembling the first-ever literature database on PPCPs.

A product central to this project is the literature bibliographic database on leftover drugs, drug disposal, and environmental stewardship (DDS). The DDS database was constructed from the main PPCPs literature database, which is the most comprehensive compilation publicly available of the resources published on the many aspects of the general topic of PPCPs as environmental contaminants. As of mid-2010, the main PPCPs database comprised over 10,000 entries. Each of the 10,000 records was assessed for its relevance to DDS. Of the total records in the main PPCPs database, roughly 1,400 addressed topics relevant in some way to DDS, and about 600 of these were journal articles (as of August 2010); roughly 600 of these 1,400 records are cited in this report. Simple text listings of the citations from both the main database and from the stand-alone DDS database (first made available for public access on 18 August 2010) are available for download at:

U.S. EPA. 2010. "Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature," U.S. Environmental Protection Agency, Las Vegas, Nevada (a comprehensive database of literature references compiled and maintained by CG Daughton and MST Scuderi; first implemented 19 February 2008); available: http://www.epa.gov/ppcp/lit.html; the direct links to the DDS database are: http://www.epa.gov/ppcp/pdf/citations-disposal.pdf [and .txt]

The complete electronic databases are available for EPA use; versions without the associated PDFs of the complete articles are available for public use. They run on EndNote (current version as of mid-2010 is EndNote X4). Information regarding the content and usage of the database is available here: http://www.epa.gov/ppcp/PPCPdatabaseSynopsis.pdf. The main database represents over 3 years of ongoing literature searching (both keyword-directed and freeform browsing). The depth of its content and the ease and speed of access cannot be reproduced even with sophisticated searching using a combination of subscription-based search engines. A particularly useful feature of the complete EndNote version of the database is that it captures web pages as they existed at the time of citing; this is useful since URLs are commonly changed, leaving the original web pages inaccessible.

The DDS database serves not just as a resource for quickly locating current information (including gaps) but also as a repository for materials that are now considered historic. The

database serves as a simple way to quickly access the published literature on any of the many aspects of the drug disposal issue, including topics as diverse as donations, recycling, poisonings, compliance, and many others. It is expected that the database could be invaluable for anyone wishing to study a specific aspect of the larger topic.

The published literature in the DDS database captures all of the archival literature, which began to first appear in the 1960s, with papers such as: Matthew (1966), Gunn and Lishman (1967), Nicholson (1967), and Robin and Freeman-Browne (1968).

The articles in the DDS database focus on several major aspects of the issue, primarily: (i) the many factors responsible for the generation of leftover, unwanted medications; (ii) surveys of the types and quantities of medications stored in the home or healthcare facilities; (iii) the approaches actually used for disposing of leftover medications (such as flushing to sewers, discarding in trash, take-back programs); (iv) obstacles to the design of optimal disposal strategies (such as existing law or regulations - the CSA being one example); (v) new legislation to allow or promote more "prudent" disposal; (vi) pollution prevention and stewardship - ways to prevent generation of leftover medications; (vii) poisonings (human and animal); and (viii) diversion and abuse.

A significant portion of the published literature is in foreign reports and journals (e.g., German, French, Italian, Spanish, Swedish). A limited, core set of publications tend to be the only ones cited in most paper (from among the hundreds that exist). Evidence exists that certain papers are cited after never having been read by the author; the same mistake is then perpetrated by subsequent authors. A case in point is the following paper, which has been cited by a number of authors but which apparently does not exist (Collins and Johnston 1992). One of the reasons for incorrect citations is that the publication source is obscure or difficult to locate.

Of most significance and critical for a complete understanding is that among the DDS articles, very few (perhaps a couple of dozen or so) provide any hard scientific data needed to support the major assertions regarding this topic. Most of these studies have been performed in a number of different countries and tend to focus on: (1) written or oral surveys of consumers regarding drug usage behavior (e.g., compliance, storage, and disposal habits), (2) inventory of medications stored on-site of homes and healthcare facilities, (3) consumer disposal practices (e.g., the route selected for discarding leftover drugs), and (4) the monetary value of unused, wasted drugs. These data might facilitate better understanding to the drivers for leftover medications, but they have not proved useful in effecting any sustainable and effective solutions.

The difficulty in locating papers relevant to the many dimensions of drug disposal can be readily seen just by considering a small portion of some of the search terms that are needed in Boolean searches to cover the entire breadth of the scientific and medical literature. Examples include: disposal, dispose(d), discard(ed), returns, returned, expired, expiry, expiration, outdated, wastage, drug waste, medication waste, pharmaceutical waste, medical waste, waste medicines, medicine cabinet, DUMP, RUM, unused, unusable, unwanted, unneeded, leftover, etc. Further complicating the need to narrow literature searching is that some of the literature relevant to household disposal of leftover drugs intersects partly with the problem of waste disposal at hospitals and other healthcare facilities - where "medical waste" primarily deals with sharps,

infectious waste, hazardous waste, and general waste; the occurrence of drugs (or APIs) in medical waste is usually viewed as incidental.

Each of the nearly 1,400 records in the DDS database was examined to determine what aspect(s) of the DDS issue it concerned; each record was tagged accordingly. The tags served as keywords, allowing fast retrieval of subsets of the database that are relevant to specific aspects of the DDS topic. They also provided some insight as to the scope of the articles in the database. Included are articles on the following aspects of DDS, all of which contribute to understanding excess drug usage, the accumulation of leftover drugs, drug disposal, or stewardship (ways to minimize wastage):

- compliance (patient non-compliance or non-adherence)
- conferences devoted to DDS
- counterfeiting (which exacerbates drug use and waste, as well as contributes to poisonings)
- destruction or encapsulation techniques (relevant to on-site pretreatment prior to disposal)
- diversion (which exacerbates drug use and waste, as well as contributes to poisonings)
- donation (redistribution for humanitarian purposes)
- expiry (API reactivity, shelf-life, stress testing, stability testing, degradation-related impurities: DRIs)
- guidance on disposal (for drugs and packaging)
- incineration
- inventory (drug stocks maintained in homes)
- legislation (governing: take-backs, disposal, CSA, Congressional hearings)
- patient behavior (including attitudes, expectations, customs, and beliefs; doctor shopping)
- poisonings (occupational, especially with regard to chemotherapeutics)
- poisonings (unintended, accidental) in humans, companion animals, and wildlife
- prescribing/dispensing (practices that increase or reduce drug wastage; polypharmacy)
- recycling (reuse, redispensing)
- sampling (free samples provided by detailing and other practices such as direct-to-consumer (DTC) advertising that increase drug prescribing)
- self-medication
- sharing (transfer of prescription drugs to those without a prescription)
- stewardship (holistic approaches for reducing drug waste)
- storage (accumulation, stockpiling, hoarding)
- take-backs

The query capabilities of EndNote allow the user to examine any aspect of the DDS topic desired. The database comprises articles published in peer-reviewed journals (about 600 total, with a representative selection in non-English languages), books and book chapters (about 50), reports (government, academic, and private sector), legislation and legal articles, local and state government documents, doctoral and masters dissertations (two dozen), conference presentations, news stories, and other gray literature (documents not readily retrievable through publishers and other conventional sources). Citations for some of the references, as cited in the publications of others, were discovered to be incorrect. Many of the resources are from obscure sources and rarely cited. Many are available by subscription only. Many are extremely difficult to locate even with intensive literature searching using Google Scholar, Science Direct, and other

resources. Nearly 500 of the 600 journal articles have PDFs of the complete article. This is extremely valuable as it provides the user with immediate access to the complete paper. Using third-party software (or the PDF search capabilities new to EndNote X4), all of the PDFs can be searched as well; file-searching software supporting line-specific Boolean searching is particularly useful.

While this is a large number of references, the vast majority cover similar ground and simply adds further confirmation to preceding studies. Few papers have offered truly new insights. By examining the resources of the DDS database, a number of insights, conclusions, and recommendations were formulated. Some of these run counter to the consensus opinions that have emerged over the years regarding leftover drugs and disposal. Some question the validity of conventional guidance regarding drug disposal. These represent major findings from this work. These were itemized in “Major Findings and Insights.”

HISTORICAL PERSPECTIVE

The issues surrounding the generation of leftover medications and their eventual need for disposal are only part of the larger puzzle that encompasses the myriad aspects of drugs as environmental contaminants. This larger puzzle exists within an even larger one of so-called "emerging contaminants" or "contaminants of emerging concern." Pharmaceuticals as a class of contaminants in the environment is a topic captured under the term PPCPs ("pharmaceuticals and personal care products"), coined by Daughton and Ternes (1999). The published literature on PPCPs and emerging contaminants has grown exponentially since the 1980s, and now comprises thousands of papers reporting on the shape, scale, intensity, and spatiotemporal aspects of the origins, environmental footprint, exposure envelope, potential for biological effects, and mitigation of PPCPs (Daughton 2009). So the topic of drug disposal must be understood within this much larger context. This larger context is sometimes ignored.

Many of the ideas for reducing the incidence of leftover medications were first proposed in the 1960s and 1970s and have been repeatedly resurrected or rediscovered in numerous studies since. Most of the very same concerns and issues regarding the storage of unneeded drugs in the home, the causes for hoarding medications (such as non-compliance), the risks associated with hoarding (such as abuse and diversion), and programs designed to collect them had already been expressed in the 1970s (and perhaps earlier) in Australia (e.g., Medi-dump and Medidrop programs) and elsewhere. Unfortunately, most of the data derived from these programs were compiled in unpublished reports (Wilks and Withers 1989).

Probably the first reported comprehensive inventory of household medication resulted from a collection event for drug waste in 1967 (Nicholson 1967): "A total of 43,554 tablets and capsules were handed in, of which 36,242 were identified."

The first major review of patient non-compliance was published over 30 years ago (Blackwell 1976). Thousands of papers on this topic have since accumulated in the peer-reviewed medical literature.

Comprehensive discussions and examinations of the role played by prescribing in the generation of leftover medications have also been underway for over 30 years (Hemminki 1975; Taylor 1978).

The increasing cost of medications and their overuse has been a topic of concern for over 30 years, prompting investigations of the types and quantities of medications that go unused in households (Leach and White 1978).

The early literature (pre-1980s) is an eye opener with regard to the issues surrounding drug disposal in the sense that few of these issues (or their solutions) are new. They are all rooted in a long history that began in the 1950s with a continual escalation in the numbers of written and dispensed prescriptions (using a widening spectrum of different types of ever-more potent drugs) for a seemingly endless array of maladies. What this shows is that many of the issues faced by drug disposal persist because the underlying causes have proved recalcitrant to any solution.

In the intervening 30-40 years, there has been little new associated with the collection campaigns currently being pursued in the US. Perhaps the only significant new aspect is the concept of using mail-backs (pioneered by the State of Maine) (Kaye et al. 2010); even the comprehensive inventory of the types and quantities of returned drugs in order to assess a number of questions surrounding prescribing, dispensing, and compliance was an objective of collection campaigns in the 1970s. Otherwise, everything is basically the same. A sense of how little things have changed with respect to collection campaigns can be gained from reading any of the older literature, such as Wilks and Withers (1989).

In the US, historical accounts usually point to the work of Kuspis and Krenzelok (1996), whose paper was the first to provide a sizeable survey in the US of drug disposal pathways. The main driver for their work was accidental poisonings (they worked at the Pittsburgh Poison Center), postulating that at least a portion of these poisonings might result from the unnecessary stockpiling of drugs or their imprudent disposal in trash. They were also among the first to point out the lack of guidelines for disposal in the US (including the State level or even from poison control centers): "It is interesting that state Boards of Pharmacy, the FDA and the EPA do not have policies on the disposal of medications when many other public hazards are under regulatory scrutiny... It seems prudent to have uniform guidelines and policies on medication disposal. Safe disposal of medications in the home should be addressed and guidelines formulated."

Even though the topic had received attention since the 1970s, and although disposal to sewers was recognized in the UK as a potential risk for the environment in the 1980s (e.g., Davidson 1989), in North America the topic began to receive very limited but broader attention only in the early 2000s, marked by two presentations at different conferences (Daughton 2003c; Smith 2002). It was not until 2004, however, that the general topic of drug disposal garnered sufficient attention to warrant focus as a topic for a conference, sponsored by the Northeast Waste Management Officials' Association (NEWMOA 2004). The Maine Benzodiazepine Study Group Conference and Unused Medicine Return Conference (http://www.benzos.une.edu/) has been held since 2002, but its early focus was on benzodiazepines, not drugs in general.

The EPA first sponsored a conference (jointly organized by the National Center for Environmental Research and the Office of Research and Development-National Exposure Research Laboratory) involving a focus on consumer drug disposal in 2005 (USEPA 2005). Follow-up EPA meetings focused on consumer disposal have included one held at Region III (excelleRx and USEPA Region III 2008). The DEA held its first conference in 2006 (DEA 2006).

Probably the earliest consensus statement regarding the need for controls on the consumer disposal of drugs was the so-called Athens Declaration (Maine Benzodiazepine Study Group 2007) [crafted by delegates at the International Conference on Environment in Athens, Greece, Aug 2007]. The Declaration codified six basic reasons to address unused drug disposal:

1. To curtail childhood overdoses
2. To restrict household drug theft
3. To limit accumulation of drugs by the elderly
4. To protect our physical environment
5. To restrain improper international drug donations
6. To eliminate waste in the international health care systems of all countries.

In 2009, the so-called Maine Declaration was proposed to augment the Athens Declaration (University of Maine Center on Aging 2009). The Maine Declaration, proposed at the 20 October 2009 International Symposium on Pharmaceuticals in the Home and Environment (Northport, Maine), articulated five, more-specific measures to achieve the basic objectives of the Athens Declaration, as excerpted here:

> To encourage a decrease in the amount of drugs wasted and a reduction in the costs of dispensing and related healthcare costs, adverse drug events, inappropriate international drug donations, and the disposal of unused prescription drugs, and in support of the Athens Declaration of August 3rd, 2007, we, a diverse group of stakeholders, support the following five measures:
> 1. Limited first-time prescriptions on selected drugs based on returns data as initiated by the State of Maine.
> 2. Opposition to financial penalties for consumers on these initial prescriptions.
> 3. Involvement of third party payers in the drug waste reduction process.
> 4. Evaluation of all aspects of refill systems used by mail-order pharmacies to reduce waste.
> 5. Participation of manufacturers, distributors, prescribers, hospitals, clinics, and pharmacies to assist with foremost improving adherence and concordance and improving patient outcomes and the reduction of medication waste.
>
> We call upon governments, NGO's, private insurers, and citizens to improve and refine dispensing policies and procedures to reduce medication waste.
> We call upon patients to recognize the need for medicine to be taken as intended if it is to be effective.
> We call upon others to endorse these principles with us for the betterment of the health of the environment and citizens in the United States and internationally.

In 2007, the World Health Organization (WHO) set forth its core principles for managing healthcare waste (WHO 2007):

> "The management of health-care waste is an integral part of a national health-care system. A holistic approach to health-care waste management should include a clear delineation of responsibilities, occupational health and safety programs, waste minimization and segregation, the development and adoption of safe and environmentally-sound technologies, and capacity building. Recognizing the urgency of this problem, a growing number of countries have taken initial steps to respond to this need. These include the establishment of regulatory frameworks, development of national plans, and the demonstration of innovative approaches. However, funding for health-care waste management remains very inadequate."

The WHO's principal recommendation is:

"The WHO core principles require that all associated with financing and supporting health-care activities should provide for the costs of managing health-care waste. This is the duty of care. Manufacturers also share a responsibility to take waste management into account in the development and sale of their products and services." In particular, "***The private sector should: take responsibility for the sound management of health-care waste associated with the products and services they provide, including the design of products and packaging***." [emphasis added]

The management and minimization of healthcare waste, while traditionally focused on infectious waste, has long had an additional focus on chemical management. This focus, however, has always been rather narrow, being limited to cytotoxics and genotoxics (and radionuclides). Rarely has any focus been applied to pharmaceutical waste in general. The management of pharmaceuticals has rarely been considered in development of sustainable healthcare (e.g., Tudor et al. 2005). But drug disposal has begun to be covered in pharmacy continuing education (Albrant 2010; Prescott and Estler 2010).

In 2009, drug disposal became a feature of the FDA's new Safe Use initiative (USFDA 2009b). Excerpted from page 14:

> "Efforts to Mitigate the Risks of Unintended Exposure. Recently, FDA announced a new effort, Disposal by Flushing of Certain Unused Medicines: What You Should Know, directed at preventing serious harm and death caused by exposure of children to certain drugs, including opioid drugs, used in the home. Unused portions of these medications must be disposed of properly to avoid harm."

Drug disposal is also the subject of ONDCP's 2010 National Drug Control Strategy (ONDCP 2010). To achieve their objective ("Curb Pharmaceutical Abuse: Preserve Medical Benefits of Pharmaceuticals"), the ONDCP notes six actions. One of these is "Increase Prescription Return/Take-Back and Disposal Programs." This action is shown as collaboration among DOJ/DEA, EPA, and HHS/FDA (page 32).

In 2010, several events will mark the first nationwide days for collection of unused prescription medications. One of these is the National “takeback day,” being coordinated by the DEA for September 25 (Cotter 2010; DEA 2010a; b).

Over the course of the roughly 5 years since the beginning of these seminal events, very substantial investments in time, money, and effort have been devoted to the topic by a wide array of public and private organizations and agencies. An extremely confusing spectrum of agencies and organizations, across all States, involved with regulations that touch upon the disposal of drugs is a major impediment to designing a streamlined nation-wide approach. Regulations directly or indirectly involving drug disposal exist at the local, city, state, and federal levels, and come under the purview of Boards of Pharmacy, departments of health, departments of the environment, DEA, FDA, DOT, etc. Myriad others are involved with issuing guidance, some of which conflicts with others. Further exacerbating the problem is that guidance and regulations for handling pharmaceutical waste in the institutional setting is mixed in with (and often confused with) the guidance and regulations for controlled substances, hazardous waste, and infectious waste.

Much of the confusion and conflicts could perhaps be avoided if one federal agency had the lead in development of disposal guidance and regulations. The major reason that drug disposal has become an orphan problem is that its origin and solution cuts across such a wide number of professions and disciplines, few of which communicate with the other.

Interest in drug disposal is witnessed by the large and increasing numbers of government agencies in numerous states and cities that now have web pages devoted to drug disposal. Because of the sheer number of participants and stakeholders, there has been substantial repetition and duplication of effort, much of it simply amounting to rediscovery or reinvention - or dead ends; some is even contradictory. This points to the need for a lead agency (or at least a national clearinghouse) responsible for setting the agenda and coordinating efforts along the many fronts of inquiry surrounding the expansive drug disposal issue.

The topic has received so much exposure via the news media and public relations campaigns from states, cities, public utilities, Congressional Hearings, and health organizations that it is now encountered in key documents not directly related to the issue. For example, drug disposal is specifically discussed in the annual report of the President's Cancer Panel; see page 75 of Leffall and Kripke (2010).

BACKGROUND AND RATIONALE

The collective actions and behaviors of those involved in the healthcare system - - from drug manufacturers, physicians, insurers, and pharmacists, to patients themselves - - often result in contamination of the environment with many of the thousands of active pharmaceutical ingredients (APIs) used in medications. APIs from human and veterinary medications are now known to be widespread and common trace contaminants in the environment - - primarily in surface waters (including drinking water supplies) but also in terrestrial settings where treated sewage is used for irrigation and soil amendment; although occurrence in finished drinking waters is much more limited, the scope of APIs known to be present in drinking waters is growing (Daughton 2010a). The potential ecological and human toxicological ramifications of chronic exposure to extremely low individual levels of multitudes (tens to hundreds) of chemically distinct APIs have not been fully revealed (Daughton 2010a). Much research has been published on the topics of environmental monitoring methodologies, environmental occurrence and fate, aquatic toxicity, and waste and water treatment. In contrast, the numerous controllable factors that contribute to, and exacerbate, the potential for exposure have been largely ignored; these largely comprise source-control and stewardship measures.

APIs can enter the environment from a broad spectrum of sources but primarily via three major routes. The three pathways of API entry to the environment are: (1) excretion of unmetabolized APIs or bioactive metabolites, (2) direct release from the body during bathing, and (3) disposal of unwanted, unused, leftover medications (and used delivery devices, such as dermal patches, still containing significant API residues). All three of these routes involve discharge via sewerage. The last can also involve domestic and municipal trash; trash can also be a minor conduit of excreted APIs from the discard of soiled clothing. Other, minor routes include direct transfer from the skin of dermally applied medications and APIs excreted via sweat to surfaces

that surround our daily lives (essentially anything that our skin comes in contact with, including other people, phones, doors, etc); this route is capable of resulting in acute exposures because of the high levels involved. These routes have been comprehensively examined in (Daughton and Ruhoy 2009a).

The sources and magnitudes of each route are critical to understand for gauging their relative importance as source terms leading to potential exposure. Excretion has been long considered as the only meaningful route of API entry to the environment, rather than disposal to sewers or release from manufacturing, but little empirical data or even modeled data exist for justifying this assumption and making it anything more than a guess. While this might be true for the roughly 1,500 APIs when considered in toto, it might well not apply when considering each API individually. After all, pharmacokinetics (namely, to what degree is an API excreted unchanged), overall usage rates, and patient compliance or adherence to medication regimes will largely dictate the importance of disposal (as well as bathing). While the disposal of leftover drugs adds to the environmental burden of drug residues, it is currently not known how significant it might be to APIs collectively or individually.

Of the many aspects of APIs as environmental contaminants, drug disposal continues to capture the attention of the public, the media, the water industry, regulators, and Congress, where several hearings have been held over the last couple of years. This attention has resulted in the proliferation of an uneven patchwork of drug take-back or collection projects across the nation. These one-time events or ongoing services allow consumers to bring their unwanted medications (subject to restrictions imposed by those medications that are controlled substances) to locations where they can be collected and "properly" disposed - generally as hazardous waste, which invariably involves landfill burial or incineration. One measure of how far the drug disposal issue has advanced is the number of laws, regulations, and resolutions passed by city, state, and federal legislators; a sampling of state statutes and bills pertaining drug returns is maintained by The National Alliance for Model State Drug Laws (NAMSDL 2009).

Perhaps an ultimate form of recognition is reflected by the Congressional resolution for "Prescription Drug Disposal Awareness Day" (Casey et al. 2010). The topic has even garnered the attention of the White House, as shown by the President's SAVE Award (Securing Americans' Value and Efficiency). The very first recipient of the SAVE award, in 2009 (The White House 2009), had proposed that the U.S. Department of Veterans Affairs (VA) reissue medications owned by admitting patients upon their discharge, thereby avoiding the traditional practice of disposing of all patient medication upon discharge. As of 2010, the VA had completed phase I of its pilot to re-label and re-dispense all patient medications.

Even approved approaches for disposal have carbon footprints. Take-back events are probably not a sustainable solution because of the costs associated with staffing and the disposal process itself. The inordinate costs associated with take-backs have been noted by many, one example being the Bay Area Pollution Prevention Group (2006), which reported $175 per person served or $450 per pound disposed. But even for larger, ongoing programs that avoid some of the costs of smaller collection events, the complete lifecycle costs associated with entire collection process have never been evaluated in a comprehensive manner. As one example, there are significant hidden costs. Unexpired but no longer wanted medications represent not only unrecoverable

purchase costs for the consumer, but more importantly, they often represent lost opportunities to have achieved their intended therapeutic outcomes. Another example is the collection of unused, unwanted antibiotics; consumption of partial treatment regimens can encourage the emergence of antibiotic-resistant pathogens. Worse yet, would formal programs for collecting unwanted drugs actually perpetuate the generation of leftover drugs by sending consumers the implicit message that leftover drugs are expected and acceptable. By facilitating easy, "cost-free" disposal of drugs with formal take-back programs, we may be inadvertently encouraging consumers to not hesitate in buying large quantities (to achieve false economies of lower unit-dose pricing), only to again find themselves unable to fully consume them before expiration. Disposal would then be followed by repurchasing new supplies - perpetuating the cycle of purchase-disposal.

Although the work subject of this report represents the first in-depth examination of the many aspects of the drug disposal pathway, it too fails to cover some of the factors governing sustainability. In a series of publications in peer-reviewed journals and books, drug disposal is examined with regard to the: (i) numerous factors that promote, control, and drive the usage or accumulation of leftover drugs, (ii) many and diverse locations in society where drug accumulation occurs and which then necessitate the need for disposal, (iii) scope and magnitude of the types of APIs that tend to be disposed (including development of the first approach for accurately identifying those APIs and their actual quantities being disposed), (iv) pollution prevention and source reduction actions and activities that can reduce or minimize the need for disposal of medications, (v) possible role it plays in the efficiency and sustainability of our healthcare system, and (vi) role it plays in drug diversion and human poisonings.

The ultimate outcome envisioned for this project could have broad consequence of national significance with regard to both the cost and efficacy of healthcare as well as the overall levels of APIs in the environment. By identifying which drugs accumulate unused, and where, how, and why they accumulate, more sustainable measures aimed at the practice and delivery of healthcare could be designed and implemented. These could not only reduce the consequent need for disposal, but also improve healthcare outcomes, reduce healthcare expenses, and reduce the incidence of diversion and poisonings. This could be done preferably not by focusing solely on ecologically prudent methods for disposing of leftover medications (the equivalent of end-of-pipe control), but rather by focusing up-stream - - changing the human and healthcare processes that lead to accumulation in the first place. The ultimate objective should be to eliminate the need for disposal altogether.

A major underlying theme that pervades the drug disposal issue is drug diversion and unintentional poisonings. It must be noted that the use of the word "accidental" in describing poisonings is ambiguous, as it often does not distinguish unintentional poisonings caused by abuse (which requires intentional exposure) from those truly caused by unintended exposure (for example, a child not realizing what they are ingesting or applying to their skin). This has significance with respect to databases on poisonings. It is not always possible to cull data from poisonings databases that are tagged as "unintentional or undetermined intent" and discern which are from ingestion with the intent for beneficial outcome (e.g., abuse, recreational usage) and which were from ingestion with no expected outcome (e.g., so-called accidental ingestions).

Medications that accumulate unused have long been suspected to promote misuse by those for whom the medications were never intended - - for recreational purposes (e.g., teen "pharming") or for abuse. Accumulated supplies of medications also increase the chances of both intentional and unintended poisonings - - not just for infants and toddlers, but also for those who have trouble remembering or following dosage instructions and where unnecessary accumulated medications serve to amplify the confusion. Stored, unused medications encourage self-medication, which can lead to fatal medication errors (FMEs) as a result of the confusion caused by the presence of multiple (or a multitude) of medications. The dual problems of diversion and poisonings were the major drivers behind the White House Office of National Drug Control Policy (ONDCP) effort to formulate the nation's first guidance for drug disposal (2009 [updated October]). It should be noted, however, that the published evidence supporting the claim that leftover, unwanted medications stored in homes (as opposed to medications in active use) are a major contributor to diversion and poisonings is sparse. This is because the portion of diversion and poisonings resulting from unwanted drugs (e.g., data inventoried by the national poison control centers) cannot be teased apart from that resulting from medications that are in current use as intended.

Ironically, the very problem the ONDCP wishes to control (primarily the diversion and abuse of controlled substances) involves regulations that also prevent an easy solution via encouraging disposal. Regulations restricting the disposal of controlled substances pose a major obstacle to formulation of a disposal system that can be easily implemented nationwide. Use of the Controlled Substances Act or CSA (DEA 2008) in the U.S. to ameliorate diversion and abuse has created a number of problems and impediments for designing disposal solutions. The primary impediment is that the CSA narrowly restricts the options for those to whom controlled substances are prescribed for transferring their leftovers; this is a result of the CSA originally having not foreseen the fact that patients would have unused drugs. These problems have only recently begun to be addressed by proposed federal regulation to amend the CSA, such as H.R. 5809 “Safe Drug Disposal Act of 2010” (Inslee et al. 2010).

One of the dichotomous problems imposed by the CSA is the opposing needs of preventing diversion of certain controlled substances (by use of the fastest, easiest, and least costly means of drug disposal - - namely flushing down the sewer) and protecting the aquatic environment. While flushing medications as soon as they are no longer needed eliminates diversion/abuse (therefore minimizing accidental and intended acute human exposures), at the same time it maximizes aquatic exposures and can lead to unwanted and perhaps unrecognized trace-level, chronic human exposure (via contaminated drinking water).

But further complicating this is that if all, most, or some APIs pose little hazard to aquatic life, flushing the most hazardous may indeed be the best approach for minimizing human exposure risk. Even those APIs that pose measurable hazard, without knowing the quantitative contributions of their disposal to total environmental loadings (portions contributed by disposal versus excretion and bathing combined), their continued flushing may not add measurably to the overall loadings. For example, if an API is extensively excreted unchanged (i.e., it undergoes little metabolic alteration or tends to be excreted as reversible conjugates) or if the API happens to be used in a medication with extremely high patient compliance (which generates

proportionately few leftovers), then disposal to sewers will contribute immeasurably small increments to total environmental loadings (Daughton and Ruhoy 2009a).

Traditionally, consumers in the U.S. have used trash receptacles and toilets for medication disposal. But, as mentioned above, two directly competing concerns complicate what initially appears to be a simple action. Historically, poison control centers have recommended that drugs be flushed down the toilet (whether leading to a septic system or to a municipal waste treatment facility) as the best means of preventing their accidental or purposeful ingestion by those for whom the medication was not intended, especially children. Although disposal to the toilet prevents immediate accidental exposure or ingestion, it unfortunately can add to the overall level of pharmaceutical pollutants in the environment (by way of treated wastewater or sludge) and consequently also holds the potential to eventually lead to extremely low-level, chronic human exposure via contact or ingestion of minute residues in drinking water (as a result of the natural "water cycle") or by ingesting food crops grown on land treated with sludge or irrigated with treated wastewater.

Without knowing the role played by disposal in contributing to the environmental loading of each individual API, risk to neither the environment nor humans can be truly assessed. Should the fail-safe approach be used - - where disposal to sewers is avoided for ALL medications - - the efficient use of resources and safest option for disposal are unnecessarily discounted.

In light of these unknowns, a new paradigm is proposed for medication usage. This paradigm seeks to solve the disposal issue while at the same time minimize the use of resources. Leftover, unused medications should be viewed not as chemical waste but rather as measures of wasted healthcare resources and as opportunities lost for achieving intended therapeutic treatments. Leftover drugs are essentially serving as messengers of critical importance to the state of our healthcare system - and the many ways in which this system could be improved. By redesigning and optimizing the use of medication, the need for disposal can be minimized. Further, by implementing systems that can readily inventory and catalog the types and quantities of leftover medications in a central database, alterations can be made to prescribing and dispensing practices that can reduce the incidence of leftovers while also improving healthcare outcomes. These data could be extremely valuable to many sectors of health care. The study of James et al. (2009) is an example of the types of data that can be collected and the types of conclusions that can be drawn regarding the causes of medication accumulation.

Finally, a potentially significant collateral benefit from minimizing the need for disposing of drugs has yet to be recognized. Although minimizing leftovers by increasing patient compliance can increase the quantities of those APIs excreted unchanged or discharged to sewers by way of bathing, minimizing leftovers resulting from unnecessary or imprudent prescribing (e.g., wrong medication) will reduce API excretion. Of the numerous facets of medical care that can be modified to reduce the incidence of drug accumulation and subsequent need for disposal, many would entail modification of dosage regimes, generally resulting in lower amounts over the course of treatment. Lower overall dosing (e.g., via evidence-based prescribing and personalized prescribing) will necessarily result in lower excretion. By taking actions to reduce the need for drug disposal, overall drug usage can decrease. Residues entering sewage from both disposal and excretion could thereby be reduced simultaneously.

If new approaches to medical care were developed that eliminated leftover drugs, the consequent environmental residues could be eliminated, therapeutic outcomes could improve, healthcare expenses could be reduced, and human morbidity and mortality (due to addictive usage and poisonings from diverted, leftover drugs) could decline. Reducing the need for disposal would also reduce the ecological footprint of medications and save on the costs associated with landfilling of hazardous wastes or incineration. Reducing, minimizing, or eliminating leftover drugs represents a very significant opportunity to improve both ecological and human health, all at reduced costs for consumers.

This project has involved the first conceptualization of a stewardship framework for optimizing the use of pharmaceuticals throughout the healthcare system. Implementing some well-targeted actions in the delivery of health care could have profound, far-reaching benefits for human and ecological health, both of which are intimately linked. By integrating ecological concerns with conventional pharmacovigilance programs (a worldwide program that tracks the detection, assessment, and prevention of adverse effects from the use of medications), a more holistic system for care of both human health and the environment could be created - - one newly termed "pharmEcovigilance" (Daughton and Ruhoy 2008a). Its implementation could reduce the cost of health care, improve therapeutic outcomes, and lessen unintentional acute and chronic exposures of humans and wildlife.

Overviews of the Drug Disposal Issue

There are many articles published in the peer-reviewed and gray literature that cover the immediate aspects of the drug disposal issue. All of these can be found in the DDS database.

Two of the first comprehensive and holistic assessments of the issues surrounding the occurrence of leftover drugs and drug collection programs are provided by Mackridge (2005) and Morissette (2006). The dissertation of Mackridge (2005) (and the ensuing journal articles) remains one of the most comprehensive examinations yet published on this multi-faceted issue.

Other comprehensive overviews, from a spectrum of perspectives, have all been published in the last 3 years (Albrant 2010; Bain 2010; Grasso 2009; Hubbard 2007a; b; Johnson 2007; Kallaos et al. 2007; Ortner and McCullagh 2010; Prescott and Estler 2010; Siler et al. 2008; Spartz and Shaw 2009; White 2010).

A series of papers co-authored by Braund (e.g., Braund et al. 2009a) provides a body of comprehensive information. An overview from the European perspective is provided by Vollmer (2010).

The National Resources Defense Council (NRDC) provides its perspective on various aspects of disposal; recommendations for future actions are on page 47 of Wu et al. (2009).

CalRecycle (2010b) has prepared a document that summarizes the many factors involved with determining the best way to handle drug waste (in California). California's SB 966 directed the then California Integrated Waste Management Board (now the California Department of

Resources Recycling and Recovery: CalRecycle) to report back to the State legislature by December 2010 with: (i) an evaluation of model collection programs for efficacy, safety, statewide accessibility, and cost effectiveness that factors in diversion of drugs for unlawful sale and use, and (ii) recommendations for potential implementation of a statewide program and any needed statutory changes.

Many overviews focus on particular aspects, such as the one from Struglinski (2009), which examines the many and conflicting obstacles and challenges facing the accumulation of leftover drugs and need for disposal (especially in LTCFs: long-term care facilities). The Product Stewardship Institute (PSI) has played a significant role in the US in advancing the dialog on drug disposal (PSI 2008a). Some of the most definitive guidance available on drug take backs is provided by the National Association of Drug Diversion Investigators (NADDI 2010).

SPECIFIC AREAS OF RESEARCH RELEVANT TO UNDERSTANDING THE ORIGINS OF LEFTOVER DRUGS, THE SIGNIFICANCE OF DRUG DISPOSAL, AND THE IMPORTANCE OF STEWARDSHIP

The following section summarizes some of what is known regarding most of the major factors surrounding the drivers for leftover drugs (origins and causes for the accumulation of unused drugs), the actual disposal of leftover drugs, and the management of drugs via principles of evidence-based medicine and environmental stewardship. Additional, comprehensive information can be obtained by searching the DDS database.

Non-compliance/Non-adherence

Introduction. The issues of drug leftovers, hoarding, and disposal have been discussed for over 40 years in the medical literature. Significantly, few new insights have emerged over these years. Little progress has been made in solving the problem. Of the many forces at work, two of the major entangled causes are believed to be patient non-compliance and the prudence of physician prescribing; these in turn are at play with an enormously wide array of other factors. The complex interconnectedness of countless driving forces makes development of prudent approaches to minimizing drug waste a risky venture, but one also having the potential for considerable positive impacts.

A topic that figures prominently in discussions regarding drug disposal is patient non-compliance (or non-adherence). Non-compliance refers to the patient's failure to take prescribed medications as directed. Non-compliance results from a patient’s conscious decision; non-adherence refers to failure to follow directions because of an inability on the part of the patient (such as not being able to remember or from confusion); the differences are subtle and they are used largely interchangeably in this document. There are many forms of non-compliance and numerous causes. The medical literature is replete with articles discussing the scope of the issue, what types of interventions might improve the incidence of compliance, and therapeutic outcomes studies (which attempt to demonstrate improved outcomes from enhanced compliance - and

degraded outcomes from non-compliance). Indeed, a search using Google Scholar for "medication AND (compliance OR adherence)" yields over a half-million records.

A major long-standing problem faced by compliance researchers is how to both define and measure compliance, which is an extraordinarily complex, multi-faceted problem with numerous variables. This is thoroughly discussed in Unni (2008) and Unni and Farris (2008).

Note that compliance is sometimes equated with adherence. These are sometimes referred to as "concordance" in the more recent literature. In reality, there are distinctions among these terms. They are often loosely used interchangeably.

The behaviors underlying non-compliance can be classified as conscious and unconscious. The former refers to purposeful deviation from prescribed directions, for any of countless different reasons. The latter refers to well-intentioned efforts on the part of patients who do not succeed or are not able for whatever reason. Unconscious noncompliance is unintentional. It can result from oversights (e.g., forgetfulness or disruption of routines, such as traveling) and from insufficient attention (e.g., taking the wrong dose by mistake).

Worth noting is that non-compliance includes both under-adherence and over-adherence (better described as oversupply). But the rate of under-adherence is usually considerably larger than that of oversupply, as shown in a study of VA patients taking psychiatric medications (Yang et al. 2007).

Non-compliance has proved extraordinarily refractory to simple solutions after many decades of efforts by the medical communities. One reason is that the causes of non-compliance may vary greatly from drug to drug. Given the vast spectrum of causes of non-compliance, and since these can vary widely among drugs, only general conclusions are possible. To have more utility in actual practice, it is probably more productive to study non-compliance and its effect on drug wastage as a function of particular categories of medications. Specific recommendations regarding expensive antiretrovirals are one example (Ostrop and Gill 2000).

While drug abuse is clearly a major threat to the public and healthcare alike, non-compliance and poor adherence to medication regimens have been called "America's other drug problem" (NCPIE 2007). The problem is worldwide, and persists regardless of socioeconomics. Even in developing countries where drugs are scarce and expensive (e.g., Papua New Guinea), non-compliance is rampant (Kiyingi and Lauwo 1993).

Compliance is an enormously important problem in medical care - one with extraordinarily large direct and indirect costs associated with excess morbidity and mortality. The critical importance of better understanding and addressing the numerous aspects of non-compliance are emphasized by Rosenow (2005), who has referred to it as the "sixth vital sign."

Sorensen et al. (2005) present a rather detailed analysis of the compliance factors associated with poor health outcomes. They found that the number of medications present in a home serves to reflect poor healthcare outcomes more reliably that the number of medications a patient is aware of taking. The greater the differential, the worse the outcomes. Large differentials reflect a higher

incidence of polypharmacy and non-compliance; large differentials indicate hoarding, poor storage practices, and forgetting that the drugs were even present. Others have also noted that poor storage strategies and accumulated medications are strongly correlated with adverse healthcare outcomes for those for whom the medications had been originally prescribed.

Non-compliance is frequently singled out as a major cause of wasted drugs. Non-compliance is also widely recognized as a major problem in healthcare, with its purported adverse impacts on achieving desired therapeutic outcomes. The cited frequencies of occurrence for non-compliance vary widely, but 50% is often asserted. But no one really knows the extent of unused drug accumulation, because of the paucity of data and the unknowns regarding generalizing across geographic locales.

The estimated portions of dispensed drugs that go unused vary immensely. In reality, there are few good data to support any reliable number. One study representative of the type of data collected is Bronder and Klimpel (2001). Equally unknown are the relative contributions from OTC versus prescription drugs (Garey et al. 2004; Isacson and Olofsson 1999). The consensus seems to be emerging, however, that the proportion of unused prescribed medications is increasing - at least in Britain (Langley et al. 2005).

Non-compliance and the problems it causes in health care and in the generation of leftover drugs is also frequently misrepresented. Data are often ambiguous or contradictory with respect to achieving therapeutic outcomes, and non-compliance does not always lead to leftover drugs - sometimes it actually prevents them.

A major assumption in the drug disposal debate has been that patient compliance (or adherence) is a primary driver for whether dispensed drugs are fully consumed as directed. A logical conclusion from this is that by improving compliance, fewer drugs will remain unused. A focus therefore tends to end up on ways in which compliance can be improved - and the ways are myriad indeed, as patient compliance is a topic that has received immense attention in the medical literature for decades (e.g., see: Gellad et al. 2009). But it is not that simple.

In reality, non-compliance cuts both ways with respect to the generation of leftover drugs. The common manifestations of non-compliance can have opposing effects on the types and quantities of drugs that remain unused, eventually needing disposal. Only a portion of non-compliant behavior involves failure to take medication. A sizeable portion deals with failure to procure medication that has been prescribed. Another portion deals with taking more medication than intended by the prescriber. Both of these behaviors result in fewer leftover medications. Some aspects reduce the problem and some exacerbate the problem. This is readily evident from some of the major findings of a survey by the National Council on Patient Information and Education {, 2007 #22097}. While almost half of those polled said they had forgotten to take a prescribed medicine (and nearly a third prematurely ceased treatment and a quarter used less than the recommended dosage), nearly a third failed to fill prescriptions they had been provided. In another study, over 20% of prescriptions languished unfilled by the patients (Jesson et al. 2005).

There are four common manifestations of non-compliance, leading to two different outcomes regarding the generation of leftovers:

(1) forget to take a prescribed and dispensed medication as directed (promotes leftovers).
(2) fail to fill a prescription (immediately results in fewer leftovers, but in the longer term, can result in the need to take more medications than originally required).
(3) take less than the recommended dosage (splitting pills or conserving doses results in leftovers and promotes hoarding).
(4) substituting OTC medication in place of filling a prescription (may result in purchase of greater quantities of medications than needed, although the APIs will probably differ).

Premature discontinuation of medications by patients is common and can occur with very high frequencies depending on the class of drug. High rates of premature cessation are frequently seen with antipsychotics, antidepressants, anti-asthmatics, and other drugs prescribed for long-term, continual usage (such as statins). Rates of discontinuation can exceed 70%. Note, however, that studies involving patient persistence and discontinuation often cite data that reflects failure to fill or re-fill a prescription, rather than failure to complete a prescription already dispensed. So overall compliance rates do not necessarily translate as a direct measure of leftover medications.

When examining compliance rates in the literature with regard to their possible impact on the accumulation of leftover drugs, it is therefore necessary to know the type of non-compliance under discussion.

Behaviors preventing the filling of prescriptions at least initially serve to prevent the accumulation of unused medications - until, that is, this type of failure to comply might lead to degraded health and the need for yet more medical intervention. But beyond this, a certain (but unknown) portion of dispensed medication should ultimately not be consumed by the patient, as compliance in these cases could lead to adverse outcomes. This includes medication that was dispensed in error (pharmacy error), medication that was prescribed in error or imprudently (e.g., physician judgment), and medication for which the patient is intolerant (e.g., adverse reactions). A certain portion of leftover drugs needing disposal therefore reflects the patient's conscious or subconscious attempt to avoid adverse health outcomes; this is referred to later as proactive non-compliance.

Further complicating the compliance-leftover drug connection are clinical and epidemiological studies that show the extreme difficulty in drawing strong connections between improved compliance and enhancement in the intended therapeutic outcomes. *After all, the ultimate objective in therapy is not perfect patient compliance, but rather the therapeutic outcome sought by the physician and patient - is the intended objective of the medication ever achieved? So a focus solely on blindly improving compliance to lessen the incidence of unused drugs is not necessarily always in the best interest of the patient.*

The "healthy-adherer" or "healthy-user" effect. Two types of scenarios loom large in the arguments surrounding measures designed to improve compliance for reducing leftover drugs. First, a host of studies over the years demonstrates an absence of improved, intended outcomes with fully compliant patients - where the medication simply did not achieve its intended effect. Second, a very significant confounding effect can complicate the interpretation of compliance-outcomes studies - known as the "healthy-adherer" or "healthy-user" effect (a

form of self-selecting bias). The healthy adherer effect is when adherence is simply a manifestation or reflection of overall healthy behavior - adherent behavior and health-seeking behaviors are directly linked. Healthy adherers might not actually be benefitting from certain medications even when it appears they are. Those with healthy lifestyles have inherent behaviors that necessarily lead to better compliance with prescribed treatment regimens, including medication adherence; a simple example is seemingly improved outcomes from adherence to preventive medications, but which instead may simply reflect existing healthy behaviors such as regular exercise. There have been numerous studies regarding the healthy adherer effect (e.g., Dormuth et al. 2009; Simpson et al. 2006), which was first noted from the data of the Coronary Drug Project (conducted between 1966 and 1975). Studies on the healthy adherer effect have shown that even adherence in placebo control groups can be associated with better outcomes compared with others who are non-adherent to active treatment. In some studies, adherence to either medication or placebo can be associated with improved outcomes.

The second deals with a portion of what first might seem like "non-compliance" but which actually results from the patient realizing that the medication is not achieving its intended outcome. This type of behavior does not have a formal name, but for the discussion here, it will be referred to as "proactive" non-compliance - that is, purposeful non-compliance aimed at avoiding a negative outcome. This contrasts with non-compliance in the conventional sense - that is, non-compliance associated with negative outcomes. A patient might display proactive non-compliance, for example, to avoid the continuation of adverse effects or because the expected therapeutic outcomes fail to emerge.

These two groups of non-compliance clearly have ramifications relevant to the entry of APIs to the environment. The first (healthy-adherers) deals with unnecessary full compliance (consuming drugs that serve no purpose), and the second deals with necessary non-compliance (avoiding drugs that do not serve positive outcomes). Healthy-adherer compliance unnecessarily adds to the loadings of APIs via excretion. Proactive non-compliance unnecessarily adds to the accumulation of leftover drugs. For both of these groups, any actions designed to reveal which medications could be avoided by either group will reduce excretion of APIs or the generation of leftovers. These actions must ultimately come from the prescriber.

These two groups of patients also show that measures to blindly improve patient compliance in order to reduce the incidence of leftover drugs may be seriously misguided as they might jeopardize the patient's health or at the least allow the continued consumption of unnecessary medications. Indeed, studies focused on interventions to improve adherence infrequently improve outcomes (e.g., see: Kripalani et al. 2007).

It is completely unknown what portion of leftover drugs result from proactive non-compliance. But proactive non-compliance is known to result from a number of factors, many of which originate with the prescriber. Effort could be devoted to minimizing the prescribing of medications in those situations for which they are ineffective or imprudent. Evidence-based (or "rational") prescribing is an ultimate goal, especially when coupled with the practice of personalized medicine, which can maximize the probability of achieving intended therapeutic outcomes (Daughton and Ruhoy 2008a). These aspects of the non-compliance issue place

responsibility not on the patient, but instead on the pharmaceutical industry, physicians, pharmacists, and insurers of health care.

Documenting an emerging understanding in the healthcare community regarding the complexity of drug wastage and the drug life cycle, the Centers for Medicare & Medicaid Services (CMS) is beginning to recognize the interconnections between imprudent or over prescribing, non-compliance, drug leftovers, diversion, poisonings, and environmental impact (Moseley 2010); see page 83, section "Encouragement of Sponsor Practices to Curb Waste of Unused Drugs Dispensed in the Retail Setting":

> "Current physician prescribing patterns and pharmacy benefit management payment practices result in most prescriptions being dispensed in 30 or 90 day quantities. Whenever the full amount dispensed is not utilized by the patient due to death, adverse reactions, medication substitution, or other reason for discontinuation, the remaining unused medication becomes waste. It also becomes an environmental hazard when disposed of, and is sometimes a safety hazard in the home or diverted to illegal use."

Some of the many causes of (and means of controlling) non-compliance. Like most aspects of the leftover drug issue, patient non-compliance can play complex and unpredictable roles. For example, if proactive non-compliance could be identified more quickly and actions taken to reduce it, the course of action might just involve changes in the types of medications prescribed rather than eliminating them.

In light of these insights regarding the possible relevance of non-compliant (or even fully compliant) behavior to the accumulation of leftover drugs, the remainder of this section on non-compliance will touch upon some of the many broad issues that may play important roles. But the published literature on this topic is immense, and the interested reader is encouraged to further examine it on their own; the DDS database is an easy place to start.

The published literature on the causes of (and possible solutions to) non-compliance is immense and cannot be covered in its whole even in lengthy review articles or books. There are two primary focuses of the published literature - the effects of non-compliance on healthcare outcomes (e.g., therapeutic endpoints) and the monetary value of wasted drugs. There are also associated concerns regarding the loss of resources that could have otherwise been put to better use (e.g., wasted time in prescribing and dispensing). Although these have proved to be the greatest motivators for better understanding the causes and solutions for non-compliant behavior, the focus here is on how non-compliance leads to the generation of leftover drugs. Only a portion of this topic can be summarized here.

Some of the notable contributions discuss how to identify and measure compliance, the causes of non-compliance, and potential approaches for its improvement (Coambs et al. 1995; Fincham 1995; Fincham 2007; Gellad et al. 2009; Kleinsinger 2010; Kripalani et al. 2007; Kusserow 1990a; Nathan et al. 1999; NCPIE 2002; 2007; Osterberg and Blaschke 2005; Perri -Year Unknown; Pound et al. 2005; Rosenow 2005; Taylor 1978; Vermeire et al. 2001; WHO 2003).

Also discussed will be some of the many ways to possibly reduce the incidence of leftovers by lessening the pressure on patients to enlist protective, proactive non-compliant behaviors.

Of the numerous causes of non-compliance, a core group tends to have been the primary focus for decades. Other causes, however, are infrequently mentioned but probably play important roles. One of many examples derives from impatience and the desire for instant gratification. For drugs that require weeks-long regimens before outcomes become evident, this group of patients often stops taking their medications after a short initial period of frustration. As one example, a drug class that experiences this behavior is acne medications for teens (Van Dusen 2008).

One of the only works to ever attempt synthesizing the voluminous information published on compliance is Pound et al. (2005). The authors note that over 200 factors have been assessed since the 1980s as causes of non-compliance. Their own study, however, concludes that the major reason for non-compliance is the patient's concerns regarding the medication itself - not because of any specific failing on the part of the patient or physician.

The comprehensive work of Mackridge (2005) covers a variety of causes for non-compliance. Several illustrate the difficulty in countering: (i) a basic dislike by the patient for using drugs, (ii) fear of becoming addicted to non-addictive drugs or of the possibility of long-term adverse effects, (iii) patient's distrust of doctors, believing that the prescribed drug is unnecessary, and (iv) patient's belief that the mere act of taking a drug verifies that the patient is indeed ill.

Cost is another little-discussed factor driving non-compliance. It has three manifestations: (i) failure to fill scripts because of high cost, (ii) desire to conserve medications for future use by hoarding, skipping doses, or splitting doses, and (iii) the sheer cost of the dispensed medication prevents the consumer from parting with leftover drugs - even when they no longer have any utility (Kennedy and Erb 2002).

Mackridge (2005) presents scenarios of drug non-use that are counter-intuitive. One involves whether the patient shares in the cost of prescribed medications versus whether the medications are provided at no cost (fully covered by healthcare providers). The former might be expected to purchase fewer medications or to purchase only what they intend to consume. But the data indicate that the former group might better appreciate the value of drugs and therefore refrain from fully consuming them - hoarding them for possible future use. This is essentially non-compliant behavior motivated by economic concerns. Patients who both overvalue or undervalue medications are prone to having leftovers.

With regard to its impact on accumulation of leftover drugs, a particularly insidious form of non-compliance involves patients with repeat prescriptions who persist in reordering solely to hide their non-compliance from their physicians. This problem is further exacerbated with the use of auto-refills by mail-order pharmacies. Some even fill prescriptions knowing that they have no intention of ever using them (often because the prescription is free or of nominal cost) (Braund et al. 2009b).

That patients have prescriptions filled but never use them was noted in a letter from a UK pharmacist nearly 20 years ago (Wilson 1991): "Today, I was asked to dispose of a large plastic bag of assorted tablets following the death of an elderly lady. I quickly realised that, far from being the remnants of her most recently prescribed medicines, the contents were, in fact, the last

four or five prescriptions that we had dispensed for her, in their entirety, with virtually no tablets consumed."

In a study designed to improve compliance with automated dose-dispensing, some users persisted in creating stockpiles and had no interest whatsoever in giving them up (Larsen and Haugbølle 2007). Indeed, most drug collection events note the surprising incidence of unused drugs in their original factory-sealed packaging - sometimes approaching 50% of the total number of packages returned (Conventry Teaching PCT 2007).

Some take-back programs report that the majority of returned medications are for long-term maintenance. Polypharmacy, largely driven by the need for concurrent long-term maintenance medications, is believed to often be a major contributor to non-compliance.

As the number of medications increases for a patient, the compliance goes down - for a wide array of reasons. A survey conducted for Medco revealed that one in four seniors take between 10 and 19 pills daily (Medco 2009a). That polypharmacy can exacerbate the generation of leftovers via noncompliance is clearly shown by the increasing rates of non-compliance once a medication regime consists merely of three medications (Van Dusen 2008).

The very young and the elderly are at the center of the problems surrounding leftover drugs. The elderly are involved with disproportionate inappropriate drug use (often resulting from confusion or self-medication) and non-compliance. Both of these problems largely emanate from polypharmacy and the confusion sown by the need for the patient to track multiple drugs, all having differing dosage directions and dosing schedules. The incidence of adverse reactions (and drug-drug interactions) also increases as polypharmacy grows larger for a patient. These factors all breed more leftover medications. These problems for the elderly all coalesce, leading to large loses in healthcare resources (wasted drugs) and enormous increases in hospitalization costs (a result of inappropriate treatments and adverse reactions). Adding to the challenges posed by polypharmacy are dosing methodologies or delivery devices that are too difficult, too uncomfortable, or too confusing to administer. Even child-resistant closures can discourage some (such as those with arthritis) from taking their medications. These are all limitations that are under control of manufacturers, prescribers, or dispensers.

Some causes of non-compliance can be directly corrected by manufacturers and dispensers. It involves consumer literacy and label design. While drug names and instructions have long been recognized as contributors to poisonings (e.g., like-sounding names), the ease with which labels can be read and understood directly impacts compliance. For example, a common problem in the misreading of labels is confusion of the dispense date with expiry date, leading to premature disposal. High rates of error have been noted when prescription container labels are translated to other languages (Sharif and Tse 2010). Functional and marginal illiteracy reduce the impact of labels. This is a factor that needs to be considered when developing proposals to guide consumer disposal via new labeling requirements (Mrvos et al. 1993).

With all of the complexities aside regarding the origins of non-compliance, one aspect is clear. Noncompliance often persists for any given patient over long periods of time before it is ever discovered by a healthcare professional. Sometimes it is never discovered. *This points directly to*

the key role that physicians could play - not with respect to preventing non-compliance, but rather with reducing its duration.

Shared decision-making and "brown-bag medication review." Increasing the visibility and awareness of the consumer/patient as an integral part of the drug life-cycle is a key objective for more effective drug usage. The linkages between humans and drug waste are downplayed to such an extent that most consumers are not aware of how the many actions, activities, and behaviors they engage in during their daily lives directly influence the burden of drugs in the environment as well as their healthcare expenses and overall health status. For example, consumers do not fully understand or appreciate the consequences of two major aspects of their relationships with medications: (i) acquisition of excessive quantities of medications and (ii) failure to consume these medications in the manner required for achieving the intended therapeutic outcomes (non-compliance/adherence). Not only do these two work against each other to maximize the magnitude of leftover drugs later requiring disposal, they often result in sub-optimal or poor therapeutic outcomes (or even jeopardize health), increase the cost of healthcare (for multiple reasons), and increase the potential for drug diversion and poisonings. Healthcare costs are increased not just because of medication waste but also because sub-optimal therapy often requires additional future medical intervention.

One of the most effective interventions for a physician to improve patient compliance is the so-called "brown-bag review" (or "medication review") which could at least be conducted periodically for patients undergoing polypharmacy. The physician asks the patient to bring all of their medications to a consultation – not just prescription drugs, but also OTC medications. This serves to also reveal those medications being prescribed by other physicians or those being unwisely purchased OTC. Preferably, the physician and patient can then work together to discuss whether any medications are no longer necessary, and adjust dosing and schedules to improve compliance. The value of this collaborative practice has been recognized for over four decades (Gunn and Lishman 1967).

The process of "shared decision-making" (SDM) is a facilitated collaboration among patient, prescriber, and dispenser. Medication reviews are just one possible aspect of SDM. This arrangement empowers and closely involves the patient in the decisions involved with their own healthcare. One of the expectations is that a fully involved patient will make decisions regarding medications that result in more efficient utilization and less wastage. An overview of SDM is available from Edwards and Elwyn (2009). In their overview, they point out numerous terms employed over the years in attempts to capture the intentions of SDM; these include: evidence-based patient choice, informed (shared) decision-making, patient-centered care, concordance, participation and partnership, informed consent, autonomy, consumer involvement and consumerism, and expert patient.

SDM especially involves more active communication between the patient and healthcare providers; one of many examples would be a patient notifying a prescriber regarding any problems they encounter while taking a medication - instead of continuing with an ineffective course of treatment or discontinuing one that they should persevere with.

One form of SDM that has gained particular attention is making a patient's medical records readily available to the patient. Providing patients easy and ready access to the medical records maintained by their primary physicians may be one way to foster better adherence to medication regimes by making patients more aware of what medications they are taking and why they are taking them. This approach has been piloted as the OpenNotes Project (BIDMC 2009; Delbanco et al. 2010).

Dispensed quantities - the roles of stat and PRN. Many of the issues surrounding drug accumulation and disposal are intimately linked to various aspects of the actual practice of medical care. A major factor often cited is the quantity prescribed and dispensed. It is therefore critical to evaluate any guidance or controls developed with the intent of reducing drug wastage so as not to degrade the quality or cost of medical care. As an example, for certain medications it might make sense to limit the quantity dispensed for a first prescription. But for long-term maintenance medications that a patient has been successfully taking, short-term prescriptions may greatly increase dispensing costs, and worse, perhaps even discourage compliance.

One of the most frequently cited ways of reducing leftovers is by dispensing smaller quantities and reducing the use of automatic refills. While these might seem at first to be logical targets for reform, the issue is far more complex and changes to dispensing practices can have unforeseen consequences. Like many aspects of the leftover drug issue, the impacts of quantity prescribed and quantity dispensed are extremely complex and a function of a bewildering array of variables, spanning patient and physician behaviors and cost.

An often cited (suspected) cause of drug wastage is longer-term prescriptions - designed for patient convenience (reduce trips to pharmacies) but moreover to reduce dispensing costs. Very surprisingly, however, few studies have ever been done to quantify the effect on wastage of reducing dispensed quantities (for example, from 90 days to 30 days). Two studies have noted that indeed larger dispensed quantities cause wastage (Domino et al. 2004; Parikh et al. 2001). The study of Domino et al. (2004) was a simulation for six different classes of drugs and showed that reducing quantities from 100 to 34 days could result in wastage reductions ranging from 5 to 14%. However, considerably higher dispensing costs would result, as well as the possibility of increased costs for the patient - exacerbated by increased transportation costs - and reduced patient compliance introduced by making refills harder to acquire. This latter issue can have adverse impacts on therapeutic outcomes.

All aspects of the drug cycle are extremely complex, often convoluted, and have intricate inter-relationships modulated by marked feedback. This is readily seen just by examining the issues in one paper associated with prescribing/dispensing (Braund et al. 2009b).

To illustrate the complexity of assessing the costs of larger - versus smaller- quantity dispensing, consider models developed to estimate the total unnecessary costs (TUC) associated with different fill quantities (usually 15-30-day vs. 90-day). These models usually account for the: (i) quantity of drug wasted, (ii) cost of the wasted drug, and (iii) costs associated with dispensing the prescription (Walton et al. 2001). Important to note, however, is that these models invariably fail to account for indirect and hidden costs, such as those associated with: (i) disposal of wasted drugs, (iii) human and animal poisonings, and (iii) environmental impact. The study of Walton et

al. (2001) found that the TUC for 90-day courses of statins was nearly half that for 30-day. But as for the absolute quantities wasted, the 90-day supplies wasted 5 times as many daily doses (5.33 versus 1.06). These data would be expected to vary among other drug classes - as the rates of physician switching treatment mid-course will differ.

Since drugs often go unused when a patient first begins treatment (as adverse effects cannot be anticipated), one common approach is the use of evaluation trials using small quantities ("trial scripts"); this is one of the roles that free samples are supposed to play. One body of evidence, however, shows that small trial prescriptions would have only a small impact on the accumulation of leftover drugs, as most leftovers do not result from new prescriptions (Ekedahl 2006).

Much has been written regarding the adverse impact of medications prescribed on a PRN basis (*pro re nata*, "as needed", "when needed", or "as the situation arises"). PRN scripts are particularly prone to result in leftover medications. Common examples are inhalable beta agonists and corticosteroids; this is also especially true for drugs formulated in dermal lotions and creams (Daughton and Ruhoy 2009a). These commonly expire before they are fully consumed. Coupled with "stat" dispensing, the two can greatly increase the chances of leftover medications.

Stat dispensing (*statim*, "immediately") usually involves all-at-once 90-day supplies of medication (Braund et al. 2007). Stat dispensing can be particularly prone to leftovers with first-time prescriptions since physician changes in treatment are more common during the initial stage of medication evaluation. This points to the possible key importance of trial scripts. Moreover, since stat dispensing results in larger quantities of drug present in homes for longer periods of time (e.g., 3 months instead of 1 month), the opportunities for poisonings (accidental or deliberate) and diversion or thefts increase.

In New Zealand, stat dispensing has increased the quantities of dispensed medications, especially those needed for long-term treatment. It has also exacerbated the portion of unused medications being disposed or hoarded (Braund et al. 2009b).

A report from White (2009a) discusses the many nuances and points of confusion regarding the data on drug wastage. White maintains that certain new policies for dispensing in Britain are mis-guided, especially requirements for smaller-quantities. These policies not only do not reduce wastage, but they cost more and jeopardize patient health. White (2010) maintains that pharmacy dispensing charges for repeat prescriptions of less-expensive generic maintenance drugs can exceed the cost of the medications themselves. White (2010) also maintains that as lower-cost generics become more frequently prescribed, the increased dispensing costs for shorter-term (1-month) repeats has the potential to eventually outweigh the estimated cost of medicines wastage in the UK. White (2009b) expresses further concern regarding one-size-fits-all policies on fill quantities, maintaining that life-long therapies have low costs associated with physician switching of prescriptions, especially for those therapies with no alternatives.

Concern over the vastly increased cost of dispensing shorter-duration scripts is certainly central to the debate. This has been documented in a number of studies over the years - all showing how

90-day supplies were much more cost effective - even after taking into consideration the cost of the wasted medications (but clearly not factoring in the unknowns regarding added disposal costs and impacts on the environment) (Brady 2005). This was one also of the many points raised in a joint letter from the American Society of Consultant Pharmacists regarding America's Healthy Future Act (ASCP 2009b).

Important to note, however, is that a focus solely on dispensing costs fails to consider the entire life cycle of a drug. It discounts the unknown costs associated with potential environmental impact. The lowering of per-prescription dispensing costs (such as by encouraging 3-month supplies), may lead to increased total cost per quantity consumed (as a result of leftover medications) and increased environmental loadings of APIs from discarded medications. Narrow assessments targeted at reducing costs at isolated, discrete points in the healthcare system often only result in shifting (or even increasing) the cost associated with other, perhaps distantly connected, points in the system.

On the other side of the debate, numerous studies have determined that smaller dispensed quantities can reduce leftovers. A study of leftover antimicrobials (many of which had been purposefully stockpiled for possible future self-medication) in the UK found that if the standard duration of treatment could be shortened and package size reduced to contain enough drug for 3 to 5 days, the temptation to stockpile might be diminished (McNulty et al. 2006). The study found that prescriptions for quantities exceeding 6 days composed 61% of leftover drugs, whereas prescriptions for quantities less than 3 days composed only 6%.

There are significant obstacles to wholesale switches from 90- to 30-day supplies. The major problems are covered by Parikh et al. (2001). The major concerns are not just dispensing costs but perhaps more importantly gaps in therapy should the 30-day course run out before the next 30-day course is dispensed. The authors showed that 30-day refills cost nearly 3 times as much as 90-day, once all factors are considered - e.g., costs associated with dispensing and mailing, even after the savings for wastage were considered.

Some maintain that both under-prescribing and over-prescribing can lead to increased needs for future treatment - with an attendant need for yet more medication and additional costs (Stroupe et al. 2004).

Mail-order stat dispensing is frequently cited as a primary origin for wastage. The relative costs and resulting wastage from mail order is very difficult to assess. Conflicting data have been reported, but the focus is generally on the impact of 90-day courses on generation of leftovers (Coster 2010; Halberg et al. 2000). But there are also other, little understood factors (specific to mail-order pharmacy), that may also lead to wastage. These include: lost, diverted, or damaged mail shipments, accelerated expiration caused by adverse conditions encountered by mail (e.g., excessively high temperatures or humidity), and failure of the patient to pick up a shipment.

To encourage the use of trial scripts ("start-up packs"), Sweden requires the same price per dose dispensed, regardless of the quantity (Landstinget Västland 2004). Trial-dispensing programs have been in effect in Canada for some time. The dollar value of leftovers dispensed in 90-day courses was found to vary among the individual medications. Changes to dispensing should first

be targeted at those medications used in the largest quantities, those that cost the most, and those known to result in wastage (Paterson and Anderson 2002). The CMS has been discussing the use of trial supplies in Medicare (The Pink Sheet 2010).

Although it might prove unwise in many cases to switch from 90- to 30-day courses, a better approach might be to begin treatment with the shortest trial course, followed by 30-day courses until efficacy is established, before finally settling on 90-day courses.

Another possible approach to minimize wastage is the use of "installment dispensing" (a variation on refills), which allows repeated dispensing of small portions of the total quantity prescribed over a set time period (Millar et al. 2003; Millar et al. 2009).

If any conclusion can be made regarding dispensed quantities, it can only be safely surmised that a number of factors must be considered with regard to each patient, the type of treatment, and the medication being employed. Across-the-board restrictions on quantities dispensed (in either direction) can have adverse consequences for therapeutic outcomes, patient health, and associated costs. Guidelines for shorter courses of medications would have to be tailored for specific drugs or classes. As one example, the State of Maine implemented a 15-day limitation of initial prescriptions for certain medications that they deemed subject to frequent switches (opiates and second-generation antipsychotics and second-generation anti-depressants) (Cook 2009; Department of Health and Human Services 2009).

Asynchronous repeat prescribing (misalignment) and inequivalence. A specific, little-recognized aspect of dispensing may have the most impact with regard to leftovers. The term "asynchronous repeat prescribing" refers to a "misalignment" between repeat prescription intervals for two or more medications; that is, two or more long-term medications are prescribed for different repeating intervals, so they often get out of sync. While this can occur when a patient is under the treatment of multiple physicians, it can also occur with a single physician. It can be particularly problematic when all of the drugs are prescribed for the same condition. A major outcome from this can be the accumulation of an excess remainder for one or more of the medications when the shortest-interval medication needs to be reordered. Another outcome can be increased non-compliance (resulting from patient confusion), amplifying the rate of leftover accumulation. Asynchronous repeat prescribing has been infrequently discussed in the literature (Clews et al. 2001; Conventry Teaching PCT 2007; Dowell and Ellis-Martin -Year Unknown).

Physicians sometimes purposefully employ asynchronous repeat prescribing when the patient wants to avoid multiple trips to a pharmacy. When one order needs to be refilled, they then wish to refill all. Note that this is no longer possible with pharmacies using databases that alert them to attempted early refills; but the pharmacist can decide to defer to the patient's desire for convenience and fill the premature prescription anyway. The Conventry report (Conventry Teaching PCT 2007) found that asynchronous prescriptions were a major cause of drug wastage. When patients had linked asynchronous repeat prescriptions, and when one ran out, they often ordered refills of the others as well, even when substantial quantities still remained.

Another related aspect of linked prescriptions is "inequivalence," where the different medications come pre-packaged in different quantities (Dowell and Ellis-Martin -Year Unknown).

Asynchronous repeat prescribing (sometimes exacerbated by inequivalence) can result in non-adherence caused by missed doses as a result of having medications running out at different times. When this occurs with long-term medications, the patient often changes their refill behavior - hoarding to prevent a possible recurrence.

In the final analysis, the major factor that encourages patient stockpiling is prescribing/dispensing policies that make it more difficult or inconvenient (or too easy) to get a prescription filled. Both can lead to stockpiling - but for different reasons.

Role of the prescriber and rational prescribing. The actions, activities, and behaviors behind the generation of leftover medications do not all originate with patients. Often forgotten is that prescribers also play significant roles (Doran and Henry 2003). Even a portion of patient non-compliance originates from physician behavior and prescribing practices. The role of the physician in drug accumulation derives from the prescribing of medications that are unnecessary or imprudent. “Presumptive prescribing” plays an important role. The impacts from prescribing when not clinically indicated span the spectrum from simple overuse of drugs to adverse reactions or poor therapeutic outcomes.

Given the essential difference between prescription-only and OTC drugs (i.e., whether self-administration is safe) (USFDA 2009a), an important irony results from the way in which prescription-only medications are actually prescribed. Lack of attention by the prescriber regarding the effectiveness or appropriateness of medications prescribed, or the prescribing of excessive quantities, increase the likelihood for the accumulation of unused, leftover drugs. Leftovers, in turn, are often used by others for self-medication. In the final analysis, by not applying sufficient oversight over the practice of prescribing, *prescription-only medications are essentially transformed into OTC medications*.

There are many reasons that physicians overlook or ignore the best practices as delineated by clinically indicated prescribing. Some reasons provided by Bellingham (2001) for presumptive prescribing include: (i) responding to the unfounded demands or expectations of patients, (ii) giving the patient unfounded expectations regarding diagnosis, treatment, or prognosis, (iii) an event indicating a clear conclusion to a consultation. Within each of these lie a number of other more specific reasons. But a major additional reason is insufficient or incorrect knowledge on the part of the physician.

A reason often mentioned for issuing a prescription is simply because the physician believes the patient is expecting one (and this belief is often unfounded) (Cockburn and Pit 1997). Patient expectations and whether a prescription is written has been a point of debate for quite some time (Britten and Ukoumunne 1997). Studies such as this reveal that a large portion of prescribing can later be deemed "not strictly indicated on purely medical grounds."

Patients' expectations can be inflated by promotional practices such as DTC advertising. If the inflated expectations are unmet, early cessation of the medication occurs - another cause of non-compliance.

In the final analysis, non-clinically indicated, presumptive prescribing is a tremendously difficult and complex problem to assess. "Rational prescribing" has been a major, long-discussed goal sought by clinical medicine, with discussions in the published literature dating back to the 1970s (Taylor 1978).

Organizations promoting evidence-based medicine such as the Cochrane Collaboration attempt to document the efficacy of drugs for intended and off-label treatments, with the intent of facilitating rational prescribing (Daughton and Ruhoy 2008a). An overview of evidence-based prescribing is given by Tamblyn (2002).

The concept of adherence/compliance is sometimes replaced by the more current notion of "concordance," which entails communication and collaboration between the patient and prescriber.

The basic questions long faced in prescribing have been whether a medication is necessary, effective, and safe. Only more recently has a new driver emerged - cost. To these can be added questions regarding the potential for environmental impact. This has been the objective of an effort pioneered in Sweden that provides the prescriber additional information regarding environmental properties, such as potential for bioaccumulation, persistence, and environmental toxicity (Wennmalm and Gunnarsson 2010).

Cockburn and Pit (1997), however, note the difficulties that would be encountered in establishing objective measures defining the "medical necessity" for a medication. The authors' study concluded that physicians prescribe more than patients expect (poor assessment by the prescriber of the patient's expectations). When patients expected prescriptions, they were three times more likely to gain prescriptions for new conditions. In contrast, when the physicians assumed that the patient was expecting a prescription, the patient was 10 times more likely to be issued a prescription: "Although patients brought expectations to the consultation regarding medication, it was the doctors' opinions about patients' expectations that were the strongest determinants of prescribing."

In 2007, the National Audit Office (NAO, London) produced a report aimed at reducing prescribing costs (NAO 2007). Portions of the report, however, are directly relevant to reducing the overall usage of medications. The report recommends a number of alterations to prescribing practices and ways to minimize drug wastage. The NAO notes, for example, that UK general practitioners generally do not receive formal training in clinical pharmacology and prescribing, despite the fact that the majority of their consultations result in a prescription. *Clearly, questions are appropriate as to whether the most prudent decisions are being made with respect to whether a pharmacologic intervention is warranted and then, whether the correct API is selected. Benchmarking of an individual prescriber's habits and behaviors against those of the profession as a whole was one recommended practice.* This can be done with the use of Morbidity Matrices, which graph prescribing volume versus prevalence of disease. These graphs readily reveal where over-prescribing is resulting in excessive morbidity. An earlier report by the HHS OIG also placed emphasis on suboptimal decisions made by physicians when prescribing (Kusserow 1989).

Rational prescribing is probably not an end but rather a journey of continual improvement. One of the ways to acquire better knowledge to improve prescribing practices would be to examine the medications that go unused. Many have advocated the key data that could be mined from detailed inventories of medications collected in take-backs. Oxley proposed that these data could at least serve to deter over-prescribing (Oxley 1996).

Costs of non-compliance (and hospital wastage). Historically, the measurement of leftover drugs has been accomplished by taking inventories within homes, hospitals, or collection events. One of the motivations for this work has been to determine the economic losses associated with wasted drugs. The objectives are often to provide the public with a more meaningful assessment of wasted healthcare resources and to spur more efficient use (such as changes in dispensing practices).

Many studies have examined the cost of wasted medications. In general, they arrive at the same conclusion - that the economic losses are substantial. The DDS database has more than 50 papers with a focus on economic losses. Only a few are mentioned here.

The monetary value of wasted drugs has been estimated for a variety of countries, including Canada, Iceland, New Zealand, Saudi Arabia, Spain, Sweden, UK, and US, among many others (Abou-Auda 2003; Åsberg 2004; Boivin 1997; Brady 2005; Craig et al. 2001; Grainger-Rousseau et al. 1999; Hawksworth et al. 1996; Orero et al. 1997; Sigurjónsson 2009).

Studies of drug wastage in both hospitals and homes extend back to the 1970s (Hart and Marshall 1976; Leach and White 1978).

Perhaps the first major report that examined the costs surrounding waste created by non-compliance was published by Coambs et al. (1995).

While the economic values can be staggering, even these estimates are usually based on the value of medications returned during collection events or on-site inventories. These estimates are therefore probably gross underestimates of the true wastage.

Many cost analysis studies have focused on wastage emanating from specific niche uses of drugs, especially in hospitals. Some of these studies have targeted drug wastage in oncology and surgery (Esaki and Macario 2009; Fasola et al. 2008). Avoidable drug wastage from anesthesia represented 26% of one hospital's entire anesthesia budget (Gillerman and Browning 2000). Incompletely used anesthesia drugs (e.g., in syringes) and unadministered anesthesia drugs can constitute over a quarter of a hospital's anesthesia drug budget (Weinger 2001). Over 30 drugs were found to be used during the study, which made a detailed inventory of 166 weekday surgeries. Those most frequently unadministered were atropine, phenylephrine, ephedrine, vecuronium, and succinylcholine. Others have also published examinations of drug wastage in hospitals (Mankes year unknown [ca 2008-2010]; Nava-Ocampo et al. 2004; Nessa et al. 2001; Törnquist 2005).

Of all the studies that attempt to calculate the costs associated with leftover drugs, none has yet to attempt a comprehensive Life Cycle Sustainability Analysis (LCSA) (Guinée et al. 2010). A

comprehensive understanding of the costs associated with leftover medications cannot be obtained by limiting the assessment solely to the retail value of the leftovers. A meaningful assessment can only be obtained by factoring other costs, including: (i) medical costs associated with incomplete treatment (resulting from patient non-compliance), (ii) disposal costs (including transport and landfill/incineration costs), (iii) costs associated with diversion (including theft) and counterfeiting (e.g., illegal repackaging of diverted drugs), (iv) unintended and purposeful poisonings (human and animal), and (v) environmental impact (e.g., landfill leachate, incineration emissions).

Technology, personalized medicine, and other approaches for improving compliance. Given the perceived importance of non-compliance to healthcare, much effort has been devoted to determine best approaches for improving patient compliance. One of the best ways has proven to be so-called “brown bag reviews” ("medication reviews" or “retrospective drug utilization review”; called "medication use reviews" or MURs in the UK), where the physician encourages the patient to bring all of their medications to an appointment, including OTC drugs (Kusserow 1990b). Although discussed as early as the 1960s (Gunn and Lishman 1967), brown bag reviews first attracted interest in the early 1980s. They have been insufficiently utilized, however, not just by physicians, but also by pharmacists and nurses. While the intent of this process is to improve therapeutic outcomes (and prevent adverse effects, such as from drug-drug interactions), it can be facilitated in such a way that medications are more efficiently used (e.g., eliminating improper or inappropriate medications or those that interact, or uncovering medications having poor compliance). Better outcomes often result in higher patient compliance and therefore fewer leftover medications. In a study of 205 patients, review of their medication stocks and consequent interventions resulted in identifying the potential for serious adverse effects in 12%, and opportunities for improving therapeutic outcomes existed for 34% (Nathan et al. 1999). Nathan et al. (1999) also present a significant number of ideas for improving compliance.

Despite the proven usefulness of medication reviews, they are resource-intensive. This has opened the door to technology-based solutions for improving compliance. Approaches span the gamut of modifying behavior to facilitating the tracking of behavior by healthcare providers.

A wide assortment of low-tech and electronic approaches currently attempt to improve compliance. Over 160 existing devices have been identified – and many more have been patented or are under development. An overview is provided by Ukens (2005). Some of the more advanced current approaches incorporate technology into the drug itself for both reminding patients and for tracking usage, as discussed by Landau (2010).

Quite a number of companies are tackling non-compliance with redesign of various facets of the drug life cycle ranging from improved packaging to better use of electronic health care records (EHRs). Basta (2010) presents a current summary of some of the major efforts underway with EHRs.

One example of the many innovative approaches is the recent advancement in "printable pills" (Canavan 2010; University of Leeds 2010). This advancement is being driven largely by the expanding array of highly potent APIs (HPAPIs), where the dose is in the microgram range.

Such low quantities make formulation of a reliable dose impossible using conventional tablet-formulation technology intended for minimum doses in the milligram range. By solubilizing or suspending the HPAPI in solution and applying it to the outside of the pill form using inkjet printing technology, the correct dosage can then be easily handled by the consumer. But printable pills offer other advantages, and some are relevant to patient compliance. For example, theoretically, printable doses could allow the creation of custom combination pills (multiple APIs, each at specific doses). This would permit the patient to take just one pill as opposed to multiple pills, a particularly valuable advance for improving compliance with polypharmacy.

Another way to improve compliance is development of long-acting formulations that require much less frequent dosing. This would be particularly useful for antipsychotics, a drug class that tends to appear frequently in unused drug collections (Velligan et al. 2003).

Regardless of the anticipated effectiveness of any technological approach for improving compliance, it may be impaired simply because of the vagaries of human behavior. As an example, consider a Danish survey regarding an automated dose-dispensing system, designed to minimize confusion caused by the complex dosing regimens often encountered in polypharmacy. On its own, the dispenser proved of no utility. It needed to be coupled with active involvement by healthcare providers (concordance) to ensure the patient understood the objectives and required commitments (Larsen and Haugbølle 2007).

Perhaps the most ambitious approach for improving compliance, but also one with the largest potential for success, is the application of pharmacogenomics and implementation of personalized medicine. An overview of this topic is provided in Daughton and Ruhoy (2010) and references cited therein. Even direct-to-consumer (DTC) genetic testing has begun to emerge in the last few years (Daughton and Ruhoy 2010; Evans et al. 2010). But DTC genetic testing has generated substantial controversy, especially with regard to quality control and interpretation of results (Erickson 2010a; Evans et al. 2010). The Human Genetics Commission (UK Government's advisory body on new developments in human genetics) has taken a proactive role and developed a framework to better ensure development of reliable and useful DTC genetics tests (HGC 2010). With over 1,600 genetic tests available for clinical use, the National Institutes of Health is planning to create a national registry (the Genetic Testing Registry: GTR) to catalog test data and applicability from test developers (NIH 2010).

Primary objectives of personalized medicine are to actively avoid the use of medications for individuals with a contraindicated predisposition (reduce adverse events and improve tolerance) and to facilitate earlier diagnosis and treatment (permitting less sustained pharmacologic interventions). One of the major attributes of personalized medicine with respect to vastly improving compliance would be removal of much of the uncertainty that currently exists in initiating (or maintaining) a medication regimen. With possession of knowledge in advance of beginning drug therapy that the potential for adverse events would be minimized and that the likelihood of therapeutic success would be maximized, patients would probably adhere to dosing regimens much more fastidiously. Increased trust or certainty by the patient in the efficacy of drugs would improve compliance. An empowered patient will be much more compliant since they will have more control over the outcomes from their own therapy. The connections between

personalized medicine and improved patient compliance have been pointed out by Castensson (2008), Daughton and Ruhoy (2009b), and SACGHS (2008).

The introduction of new technology also has the potential to worsen non-compliance. One example is the use of automated dispensing machines for public use (Lever 2010). Vending machines for dispensing repeat prescriptions directly to consumers are being evaluated in Britain. Dispensing without the interaction of a pharmacist, however, was found to increase the chances that a patient will misunderstand dosing directions and the chances of dispensing errors not being caught.

Redesigns targeted at any of the processes or features of the existing life cycle of medications, as well as the implementation of new technology never before used, or creation of new drug formulation or delivery devices can all make major contributions toward improved compliance and reduced leftovers. These advancements, however, must be done by incorporating principles of sustainability and green design. This wide spectrum of approaches have been discussed (Daughton 2003a; Daughton and Ruhoy 2009b; 2010).

Leftover drugs as contributors to human poisonings

The potential for poisonings from improperly discarded medications has long been known. One case study was published over 50 years ago (Jacobziner and Raybin 1959): "This child was playing out-of-doors with another child. They found many medicine bottles with different colored pills in them in the public garbage bin on the grounds of the housing project in which they lived. Thinking the pills were candies, the child swallowed several of the different pills from the various bottles. ...This accident certainly could have been prevented if more caution were exercised in discarding unused drugs."

Human poisonings resulting from stored medications is a concern in numerous countries, as reflected by the international breadth of the literature. The DDS database contains over 130 studies regarding poisoning, from countries worldwide.

The potential for drug poisoning (excluding suicide) can involve a number of different scenarios, many of which involve death or gross morbidity. Three primary scenarios are:

(1) accidental poisonings - such as infants and toddlers coming into contact with new and used medications (primarily ingestion or dermal contact);

(2) unintended poisonings - purposeful ingestion without prior knowledge for potential effects (e.g., diversion by teens); an important factor in unintended poisoning but rarely discussed is medications that hold little hazard for the intended patient but which pose great hazard for those not intended for the drug; certain at-risk sub-populations cannot be exposed to certain drugs (examples are drugs under restricted distribution programs, such as isotretinoin and thalidomide);

(3) therapeutic misuse (inadvertent poisoning) - such as the those who might be confused by drug names or those involved with polypharmacy regimes; these commonly involve the elderly.

Two age groups account for nearly all unintended poisonings by medications - the young (under 5) and the older (over 65). While the risk factor for the former is inquisitiveness, the factor for the latter is forgetfulness - leading to over-medication or dosing with the wrong medication (medication errors). The older age group is also a factor in exacerbating poisoning for the younger because of the higher frequency with which medications get misplaced (forgotten), dropped, or disposed improperly.

Showing the highly refractory nature of the problem, poisonings of children by medications has long been recognized as a major cause of morbidity (and sometimes mortality). Many of the same concerns, recognized causes, and proposed solutions have remained unchanged for decades, as shown in a 1966 report (Matthew 1966).

Estimates for the US (from 2004 to 2005) show that annual unintentional medication poisonings in children younger than 18 exceeded 70,000, nearly double that for unintentional poisoning by all non-pharmaceutical products; while this includes medication errors (overdoses), it is undoubtedly an underestimate as it included only those cases presenting to an emergency room (Schillie et al. 2009). The rate of subsequent hospitalizations was 4 times higher for pharmaceutical ingestions. Over 80% of poisonings were from unsupervised medication ingestions. Over 80% of these cases were among children younger than 5, with the highest rate among 2-year olds. The most common APIs involved with unsupervised ingestions were oral medications (usually available OTC), including acetaminophen, non-opioid and noncarbinoxamine cough and cold medications, NSAIDs, and antidepressants. OTC medications were involved in over a third of the poisonings.

Schillie et al. (2009) note that drug poisoning data also likely underestimate the incidence that is not captured by emergency rooms, such as when patients do not receive medical attention (especially those who die prior to receiving medical attention). They emphasize that "Medication overdoses among children, notably unsupervised ingestions, represent a substantial public health burden in terms of emergency department visits and hospitalizations."
It is generally agreed that the incidence of poisonings published by a wide spectrum of organizations worldwide is lower than the actual incidence - primarily because of under-reporting (for example by clinics, doctors, and parents) and the difficulty in ascribing morbidity and especially mortality to ingestion of a particular drug.

Accidental poisonings are classed as a subset of adverse drug events (ADEs). In a 2-year sample, nearly 160,000 annual emergency room visits for ADEs were made for patients under 18 years old. Nearly half were 1-4 years old, and roughly 45% were for unintentional ADEs. Nearly half of the ADEs were caused by antimicrobials (25%), analgesics (14%), and respiratory medications (11%) (Cohen et al. 2008). Acetaminophen is particularly problematic, as emphasized by Daughton (2003c). A good overview of the drugs most commonly involved with poisonings (in the UK) is presented by Greene et al. (2005). Many citations of published accounts of accidental poisonings in children are available from Geib et al. (2006).

While it has been long established that drugs are a major cause of poisonings, especially among young children, it is rather surprisingly that it is not known what portion of these poisonings occur from contact with, or from ingestion of, drugs that are no longer being actively used for

their original intended purposes. These include drugs that: (i) have expired and should have been disposed, (ii) are being stockpiled (perhaps indefinitely) for future disposal, (iii) are awaiting imminent disposal (regardless of the route by which they will be disposed), or (iv) have been imprudently disposed (especially in the trash). Such leftovers must be distinguished from drug stocks that are still in active, current use for their intended purposes and which would not be subject to disposal. In the absence of being able to distinguish those drugs no longer needed from those that are, it is not possible to determine whether programs designed to facilitate households in getting rid of their drugs no longer legitimately needed can be effective in reducing unintended poisonings.

Even more difficult is to assess is what portion of unwanted drugs improperly disposed or improperly stored are diverted and then contribute to abuse. The absence of any study attempting to link poisonings with the improper disposal of medications (or the stockpiling of useless medications that should have been disposed) is striking, as this would be a major evidence-based driver to justify the implementation of steps designed to reduce the incidence of drug accumulation in households.

Significantly, no study was located that had tried to distinguish in-home drug poisonings caused by medications still being used therapeutically versus those that are no longer being used and which should be disposed or that are awaiting disposal. The sole exception is poisonings caused by transdermal patches (see section later below) that have been used but not properly disposed. Such data are available in one of the only surveys (unpublished) to date, which revealed that of the 10% of Washington/Oregon residents who knew someone who had been accidently poisoned by a household medication, 13% said that the poisoning resulted from a medication that was expired or unwanted (Whittaker 2010; see slide 19).

Of the published reports on poisonings by transdermal patches, several have involved used patches. Of those involving used patches, one could assume that at least a portion of these have resulted from patches that were either improperly disposed (e.g., in accessible trash) or that had not yet been disposed (e.g., left on countertops); some poisonings by used patches result not from discarded patches, but rather from patches still applied to the body but accidentally transferred to someone else (such as when sharing a bed). As an example anecdote from one report: "...callers commonly reported that the child was found with a disposed patch, which often contained a large amount of medication, in his or her mouth" (Parekh et al. 2008). But similar anecdotes for delivery devices other than patches were not located in the literature. An overview of drug poisonings is presented in Daughton and Ruhoy (2009a).

It may well be that a possible linkage between poisonings resulting from unwanted versus in-use medications can only be tested in prospective studies. Such a study would involve locales having extensive bodies of historical data on drug poisonings. After implementing programs designed to facilitate the rapid removal of all unwanted medications from homes as soon as possible, a drop in poisonings should be readily apparent if unwanted medications play a significant role. But few studies have ever attempted to establish whether childhood poisonings decrease even after a large-scale take-back event. Two of the only such studies were conducted in the 1970s (Bradley and Williams 1975; Harris et al. 1979) and involved some of the largest take-back events ever conducted before today's renewed interest. For example, from the work of Harris et al. (1979):

"In a returned-medicines campaign lasting 3 weeks 362 000 tablets and capsules were returned in 11 400 containers from a population of 1.5 million."

The following sections discuss the major aspects of human poisoning that are related to leftover drugs and disposal.

Data from poison control centers and coroner reports

Data for studies that attempt to estimate the contributions to human poisonings from medications come primarily from the Poison Control Centers (AAPCC 2010). Few studies examine all sources of poisoning records to ascertain the incidence of unintentional fatal poisonings. In Sweden (Jönsson et al. 2009), drug poisoning fatalities are relatively common, with the incidence of unintentional poisonings roughly less than 5 per 100,000 person-years in the general Swedish population; benzodiazepines, antihistamines, and analgesics are most commonly involved. These rates apparently reflect those worldwide.

The paucity of data needed to directly link poisonings with imprudently disposed or stored leftover drugs is primarily a consequence of the information collected during (or mined from) investigation of accidental poisonings. Poison control centers generally exclude notation of the storage location or whether the drug has expired. When considering data on fatal poisonings compiled by poison control centers, it is important to keep in mind that these data are not comprehensive, as they often do not contain data from coroner reports and many other sources; one estimate is that they capture perhaps only a quarter of the actual incidence of cases (Roberge et al. 2000).

Coroner reports can provide a rich array of data, including whether a drug has expired. The types of data that can be mined from coroner reports are discussed in Ruhoy and Daughton (2007). Mining data from death certificates has also been discussed by Wysowski (2007).

The creation and growth of the Poison Control Center movement in the US is captured in an historical exhibit at the Duke Medical Center, which served as the nation's second Poison Control Center. The Duke Center was established in 1954 and was involved with development of the first safety cap (for Saint Joseph's aspirin); aspirin had been made more appealing to children in the 1940s with the addition of flavorings, and was responsible for a quarter of all childhood poisonings in the 1940s-50s (Duke Medical Center Library & Archives 2010).

Drugs are historically one of the leading causes of poisonings each year, worldwide. Until 2007, poison control centers had long-advised against discarding leftover medications to domestic trash and had instead favored discarding to sewers. Disposal to sewers had historically proven the best way for protecting human safety - preventing accidental poisonings of children, adults, and pets, as well as purposeful ingestion by those for whom a medicine was not intended. As a consequence, even the newest disposal guidance issued by the FDA (USFDA 2009 [revised March 2010]) continues to recommend the disposal of certain hazardous drugs or those likely to be diverted and abused, by flushing down the sewer. Although the pressure grows from a wide spectrum of stakeholders to discontinue the disposal of all drugs to sewers, the major question is

really whether this list is sufficiently comprehensive as to include all the medications that pose acute risks associated with diversion or poisonings if disposed to trash? The question might not be whether to discontinue disposal to sewers, but rather, whether disposal guidance should include recommendations to flush yet more drugs. In the final analysis, the decision to flush or to dispose to trash could be based not just on whether a drug poses extreme risks to human safety but also on whether flushing would make significant contributions of a particular API to the environment. This is a function of the pharmacokinetics of each API (Daughton and Ruhoy 2009a). For those APIs that are excreted largely unchanged, disposal of these drugs to sewers might contribute negligibly to environmental loadings. In contrast, for those APIs that are extensively metabolized, disposal to sewers could prove to be significant of these APIs in the environment (Daughton and Ruhoy 2009a).

Factors that can exacerbate poisonings - the roles of packaging (especially child-resistant closures - CRCs), drug design, and consumer behavior

Other than the toxicological nature of the API (some being very potent or having very narrow therapeutic windows), several factors serve to increase the risk of poisonings by drugs. Most of these factors pertain to infants and children, as medications have long proved particularly attractive to children.

Drug packaging and container design play direct roles in drug waste; this is discussed in a later section. The design of packaging also plays dual roles in poisonings - by encouraging and facilitating poisonings and also by preventing them.

The overall design of packaging can make drugs more attractive to children. The color, taste, odor, shape, and graphics of the medication itself can also enhance the attractiveness of drugs for children. This is true even for certain veterinary medications, which are often flavored to encourage pets to consume their medications.

Adults can unwittingly contribute to childhood poisonings. Adults referring to medications as "food" or "candy," or as "tasting good," in efforts to encourage children to take needed medications can enhance the attractiveness of leftover drugs and promote drug-seeking behavior (Chatsantiprapa et al. 2001). For the same reason, adults are encouraged to refrain from taking their own medications in front of children, as children will also try to mimic the drug usage behavior of adults (Massadeh 2007).

A major exposure factor governing children's exposure and how children intentionally access or accidentally encounter drugs is the spatial location of medications - not just the household room location but the spatial elevation. More data could assist in better focusing countermeasures. Not surprisingly, storage of drugs in the kitchen (especially the refrigerator) promotes poisoning in children. The considerable numbers of surveys of home inventories and their possible relationship to unintentional poisonings have rarely ever collected data on spatial elevation or accessibility of the medication within particular rooms (e.g., Kaufman et al. 2005; Smolinske and Kaufman 2007).

One of the most extensive studies of medicines stored in homes is also one of the only to examine differences between countries in the types or drugs stored and their locations within the home (Sanz et al. 1996). The numbers and types of medications, and the locations in which they were stored, were found to vary widely between and within countries. Interviews with children from all locations studied said they had access to home medications. Medications were commonly found stored with foods.

Regardless of the controls placed on preventing access to children, two key risk factors are (i) those medications that are in active use and therefore might not be securely stored, and (ii) those medications that cannot be stored because they have been forgotten (polypharmacy and stockpiling are contributors to this problem). Many retrospective poisoning studies reveal a correlation between the incidence of poisoning and the expiration of the medication. The reason, however, does not derive from toxicity of expired drugs, but rather that expiration of a medication is an indicator of imprudent storage (since the medication has been kept too long) (Margonato et al. 2008).

Surprisingly, few studies have focused on storage behavior as a function of consumer beliefs regarding toxicity. Little is known regarding the factors that might influence consumer behavior for the storage of specific medicines. Perception of toxicity (irrespective of reality) seems to dictate the likelihood of where a medication will be stored. A select number of medications perceived as being toxic were more likely to be returned to their normal (secure) storage locations immediately after use, as well as being stored more safely. OTC medications, being perceived as less toxic than prescription medications, were less likely to be safely stored (Patel et al. 2008). The inherent toxicity of certain OTC APIs, such as acetaminophen, coupled with the perception that they are not hazardous, perhaps partly explains why certain OTC drugs are almost always involved with the highest numbers of unintended poisonings (USFDA 2010a; Woodcock 2009).

Household poisonings of young children (2 years of age and younger) is unquestionably a major cause of morbidity and mortality from accidental poisonings. These poisonings commonly involve opioids, especially methadone, oxycodone, and hydrocodone (Bailey et al. 2009). The elderly, however, suffer higher rates of hospitalization and death from poisonings compared with children (Haselberger and Kroner 1995).

An irony noted by Bailey et al. (2009) is that although "medications are often labeled 'keep away from children,' no products to our knowledge note extreme danger, such as warning that 1 pill can kill a young child." *The critical importance of understanding the extreme risks posed by drugs that can be fatal in a single dose is covered in a section below. This is perhaps the major factor that should be evaluated in future considerations for revising drug disposal guidance.* The lethal potential of many medications (those designed for administered via the skin were summarized for the first time in Daughton and Ruhoy (2009a).

In a study by McFee and Caraccio (2006), 10 to 20% of unintentional pediatric poisonings in the US were found to involve grandparents. The authors referred to this as the "granny syndrome," for the propensity of non-parent medications to be left unsecured.

The elderly are particularly prone to accidental poisonings, in part because of confusion caused by excessive numbers and quantities of stock-piled or hoarded medications. Polypharmacy is a major factor that exacerbates unintentional poisonings in the elderly. Unintentional poisonings in the elderly often involve drug dosing errors, incorrect medication, incorrect route of administration, and toxicity from long-term use (including self-medication) (Cassidy et al. 2008; Haselberger and Kroner 1995).

A 2009 national survey conducted for Medco of those over 65 and taking medications, found that 51% take at least five different prescription drugs; one quarter take between 10 and 19 pills daily (Medco 2009b).

Adding to the overall burden and hazard of medications in the home is the availability of highly toxic and expired medications available from Internet auction sites (Cantrell 2005).

Child-resistant closures (CRCs). The Poison Prevention Packaging Act of 1970 (PPPA), 15 U.S.C. §§ 1471-1476, is administered by the U.S. Consumer Product Safety Commission (CPSC). The US CPSC issues the regulations governing those aspects of packaging that impact the potential for poisonings. For most oral prescription drugs, the PPPA requires child-resistant packaging (which must also be adult-friendly) (US CPSC 2005).

Although the numbers of deaths annually for children younger than 5 years who are unintentionally poisoned is low compared with most other causes (about 30) as reported by the US CPSC (2005), this number becomes a critical consideration when disposal guidance is designed with the primary objective of reducing APIs in ambient waters to below their already minute levels - and especially when redirection of API disposal away from sewers has an unproven impact on these trace levels. Furthermore, disposal guidance that directs consumers to transfer their medications from original special packaging (e.g., CRCs) to containers that are less secure circumvents the intent of CRCs.

Despite the reductions in childhood poisonings attributed to the advent of child-resistant packaging, this special packaging has proved surprisingly controversial over the years. Many studies show a positive impact on reducing poisonings, while others have shown no effect.

One source of this controversy is that the efficacy of CRCs in reducing unintended poisonings in children is complex to measure. Long-term post-hoc studies require rigorous controls for a wide variety of other factors unrelated to CRCs. One study showed a 45% reduction in poisoning mortality in children younger than 5 from the period 1964 through 1992 (Rodgers 1996); this translated to a total national annual reduction of 24 deaths (changes in morbidity were not assessed). This study also found that 50% of all poisonings from oral prescription drugs may have involved "medicines either originally dispensed in conventional non-child-resistant packages or in child-resistant packaging that has been disabled."

A study by Franklin and Rodgers (2008) determined that about 55% of poisonings may have involved child-resistant packaging. Other studies have also shown CRCs do not have any effect on the incidence of childhood poisonings (e.g., Hon et al. 2005; McFee and Caraccio 2006).

One source of CRC failure seems to be inadequate understanding of how to (or inability to) properly re-close a CRC. This possibly reflects poor design (for example, inadequate sensory feedback for the user signifying when the CRC is fully closed) or inadequate consumer education or capability. An in-depth examination of closures is provided by Sherrard et al. (2005).

One force that might be in play to either work against or promote development of better CRCs is the predicted growing demand by seniors for packaging that meets a whole new spectrum of needs. The baby boomers "do not want their pharmaceuticals to look like pharmaceuticals." The desire is for packaging that no longer resembles conventional screw-cap drug containers, but which is instead more stylish and easier to carry, and at the same time promotes better compliance (Valigra 2008). More stylish containers, however, could prove even more attractive to children, so child-resistance will need to be enhanced.

For those with impaired hand-strength or poor dexterity, the current generation of CRCs can actively discourage compliance, leading to leftovers. CRCs and polypharmacy can conspire to frustrate and confuse the elderly, sometimes resulting in consumption of unintended medications that should have otherwise been discarded.

Single-dose lethality and fatal medication errors (FMEs) at home. Some drugs pose extreme risks in acute poisonings. Some are mutagenic or teratogenic. Some can be fatal in a single dose. *This is perhaps the major factor that should be evaluated in future considerations in revising drug disposal guidance*.

Drugs possessing the potential for single-dose fatality require special consideration in disposal options. Very real acute poisoning risks are posed by improper disposal of drugs that can be lethal at single doses, not just in children, but also adults. These APIs include not just those used in oral dosage forms, but also those used in certain transdermal and other drug delivery devices (e.g., medicated patches - see section below). Transdermal devices pose extreme hazard even after their use is complete; as one of many examples, after 3 days of use, fentanyl patches can retain up to 84% of their original fentanyl content, a more than sufficient fatal oral dose for an infant or fatal dermal dose for an opioid-naive adult. Drugs with single-dose (or low-dose) lethality should never be left unsecured - wherever they are located including the trash. This topic has been covered for the first time by Daughton and Ruhoy (2009a).

The fact that a number of different medications can be fatal in children following ingestion of a single dose demonstrates the extremely hazardous nature of disposal guidance that encourages consumers to handle their medications more than absolutely necessary. This includes any practice - even if intended to facilitate "safe" disposal - that involves the removal of medications from their containers. It is critical to recognize that any mistake that results in a single tablet falling unnoticed to the floor or other surfaces accessible to children poses grave risks.

A perspective regarding drug lethality can be gained by comparison with pesticide toxicities. Lethal doses in humans for pesticides are often rated on a scale where the two most lethal groups have LD50's of less than 1 mg/kg (extremely toxic) and 1-50 mg/kg (highly toxic). But keep in mind that these are two classes are no longer sold for home use; because of their extreme toxicity, they are available only for use by professionals. If we examine fentanyl (or a number of

other drugs not uncommonly available in homes) (Daughton and Ruhoy 2009a), we see that they can be lethal to children in doses of mg/body - one or more orders more toxic than the most toxic pesticides. Given that the less-toxic pesticides used by consumers are rarely stored inside homes, the gross disparity in the way which these hazardous medicinal substances are treated is evident.

Some of the many medications that can be fatal to a 10-kg toddler ingesting only 1 or 2 tablets or teaspoons include common ones such as: chloroquine, hydroxychloroquine, imipramine, desipramine, quinine, methyl salicylate, theophylline, thioridazine, and chlorpromazine (Bar-Oz et al. 2004; Koren 1993; Lex -Year unknown; Matteucci 2005; McIntosh and Katcher 2005; Morris-Kukoski and Egland 2009; Osterhoudt 2000).

It can sometimes take a while for sufficient poisoning data to accumulate to fully appreciate the acute toxicity potential for certain drugs. An example is calcium channel blockers (especially nifedipine and verapamil), which have been involved in a growing number of unintentional poisoning cases in children. Exposure-toxicity response data are confusing, but one report concludes that these medications can sometimes be fatal in children at a dose of a single pill. No antidote is available, and the onset of mortality can be rapid (Ranniger and Roche 2007).

The opioids are a class of drugs posing major concerns with respect to poisonings. Fatalities from poisonings in children are most common with hydrocodone, morphine, oxycodone, and propoxyphene. Methadone is one of the most toxic opioids. In children younger than 6, a single dose can be fatal (Sachdeva and Stadnyk 2005).

Arguments have been made for the need for special warning labels for medications that can be fatal in low doses. Much could also be done to reduce access to medicines by young children, especially by: (i) designing child-resistant closures (CRCs) that are more difficult for children to open while being easier for older adults to open and fully close, and (ii) making medications less attractive to children by modifying the taste, odor, appearance, and packaging.

An overview of childhood poisoning by drugs and prevention measures is available from Ozanne-Smith et al. (2002).

Finally, the potential for unintended poisonings to result in serious morbidity or mortality is the central concern to the FDA in its current drug disposal guidance. But concerns regarding a limited number of medications require that they still be immediately flushed into sewers following use (Daughton and Ruhoy 2009a). This requirement has bred considerable confusion for the consumer, as prudent disposal guidance is not necessarily straightforward (e.g., Hornback 2007).

Transdermal and topical drug delivery systems (TDDS). Insights regarding which APIs should be targeted with respect to the hazards they pose as leftovers and during disposal can be gained from examining case histories published on childhood poisonings. This was done in the discussion above for those drugs that can kill in a single dose. Many of these cases involve APIs used in transdermal and topical drug delivery systems (TDDS). TDDS have certain therapeutic properties superior to those of oral medications. For example, the delivered dose avoids the possibility of poor GI absorption, the API bypasses first-pass metabolism, the API can

achieve a constant systemic level, for long-acting APIs the dose can be removed from the body, and patient compliance can often be improved. These properties have served to continually increase the popularity of TDDS.

Among the types of TDDS, however, transdermal patches have posed some special concerns. The literature is replete with case histories involving acute poisonings (especially infants and toddlers) by medical patches, pointing to the critical need for much better guidance for disposal of this special class of medications. These particular medications point to how generalized guidelines for disposal may lead to the less-than-optimal and non-timely disposal of extremely hazardous substances.

This topic, with a focus on transdermal patches, was covered for the first time with respect to its relevance as a source for environmental contamination by Daughton and Ruhoy (2009a). An overview of how transdermal devices or systems are designed and work is provided by Ball and Smith (2008).

While TDDS in many circumstances eliminate the need to dispose of syringes, they pose a new challenge for disposal of the device. Also, while transdermal delivery makes lower systemic doses possible (by avoiding first-pass metabolism and poor GI absorption), and therefore can sometimes lessen the excretion of unchanged API, it actually increases the total quantity of API required in the device because of the incomplete absorption across the skin. This means that significant quantities of API residuals can remain in used devices; from 10-95% of the initial API content can remain in a transdermal patch that has been completely used as intended (USFDA (Leslie Kux) 2010). These residuals are eventually disposed along with the device. The API residuals in used TDDS pose more of a risk with regard to accidental poisoning than do syringes because they can be accidentally ingested or contacted with the skin.

Some of the existing instructions for disposal of used patches (or new ones that are no longer wanted) may be misguided. For example, cutting patches into pieces prior to disposal to trash could increase the hazard should accidental ingestion or exposure to the skin occur (the routes of exposure reported for young children and infants). This is because puncturing the device destroys the drug reservoir integrity in the patch, making the highly concentrated API much more readily available for absorption should inadvertent exposure occur.

An overview of the complexities and hazards associated with TDDS is presented by Roberge et al. (2000). Historically, unintentional poisoning from transdermal patches has been dominated by clonidine, fentanyl, and nicotine. Some cases of poisoning specifically from clonidine patches are summarized by Klein (1991).

The study by Roberge et al. (2000) is unusual in that it provides data on poisonings actually caused by retrieval of used TDDS from waste containers. The authors emphasize that the growing popularity of TDDS, coupled with the formulation of yet more distinct APIs into TDDS, will probably mean the incidence of poisonings will increase without better preventative measures. The problem is exacerbated even further when TDDS are switched from prescription-only to OTC. The greater availability then increases the probability of accidental exposures. This is evident with nicotine patches, which were switched to OTC status in the US in 1996 (Woolf et

al. 1997). An 11-year was poisoned by nicotine after applying a patch to his arm (Wain and Martin 2004).

Other more-potent delivery formulations of fentanyl periodically enter the market place. These dosage forms pose extreme hazards for those who are opiate naive and who may experience incidental exposure. One example is the fentanyl buccal soluble film, BEMA fentanyl (marketed as Onsolis in the US), which is used to treat break-through pain. These highly hazardous drugs are required by the FDA to have a REMS (Risk Evaluation and Mitigation Strategy) - - a strategy and plan for ensuring that risks are outweighed by the benefits (Olin and Ziglar 2010; USFDA 2010a); also see the following links:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm;
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163655.htm;
http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM163668.pdf;
http://www.drugs.com/nda/onsolis_080828.html#ixzz0t6NkyH00;
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220952.pdf.

Development of REMS, however, is not straightforward because of the potential for impacts across a wide range of stakeholders. This is reflected by the long discussion regarding the FDA's proposed REMS for Extended-release and Long-acting Opioid Analgesics, which was held in July 2010
(http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM220470.pdf).

The dose equivalents remaining in used transdermal devices is summarized by Daughton and Ruhoy (2009a). As one of many examples, an excess of a fatal dose of fentanyl remains in patches that have been used for 3 days (Marquardt et al. 1995).

Prudent disposal guidance that provides specific instructions for TDDS could therefore play a major role in reducing the incidence of poisonings. Given the extremely hazardous nature of transdermal devices, it is very noteworthy that they are rarely mentioned as special cases in the guidance for conducting drug take backs. One example is the guidance provided by the National Association of Drug Diversion Investigators (NADDI -Year Unknown).

The critical importance of ensuring immediate and secure disposal of used patches is shown by the death of a 1-year old after ingesting a fentanyl patch found lying on the floor. This fatal poisoning occurred after the grandmother thought she had disposed of a fentanyl patch (after 3 days of proper use) into the trash but had not noticed that she had instead dropped it on the floor (Teske et al. 2007). *Cases such as this clearly show that when handling a drug (for whatever reason), a single mistake can ultimately lead to death. This is why disposal guidance that fosters unnecessary handling or drugs (including transfer among containers or alteration of physical form) is misguided.*

Even manufacturers' guidance for transdermal patches does not ensure safe disposal if other factors are not considered. As an example, a 9-month old was poisoned after he placed a discarded dermal patch containing clonidine in his mouth. The patch had been used constantly for 5 days prior to properly folding in half and then discarding in the trash, as instructed by the disposal instructions (Caravati and Bennett 1988).

Because of the route of administration and the nature of the device, transdermal patches may be perceived by patients as inherently safer than oral medications. This perception, for example, may have contributed to the death of a child after a "caregiver applied 3 of her fentanyl patches to a 4-year-old child because she knew it helped with her own pain" (from: Parekh et al. 2008).

Used fentanyl patches are known to be reused, such as by abusers. One of many reported cases involved the reapplication of used patches by a funeral home worker who had removed them from a decedent (Yerasi et al. 1997). The extreme hazard of fentanyl in transdermal devices is shown by its toxicity even among drug abusers when used orally (Woodall et al. 2008).

Dermal patches, unlike most oral dosage forms, can also pose acute risks merely from being handled. A child need only hold a used patch to achieve a significant level of exposure. Even the routine and proper handling of patches by caregivers has the potential for exposure via dermal contact (Gardner-Nix 2001).

Worse yet is application by children of a used patch to the skin or placing the patch in the mouth followed by chewing, sucking, or swallowing. The ease and variety of ways that patches can cause inadvertent poisonings is shown by the report of a 2-year old poisoned with fentanyl after a 5-mg patch being worn by his grandmother accidentally transferred to the child's back while the two shared the same bed (Hardwick et al. 1997). The patch was no longer at full dose as it had already been worn by the grandmother for 36 hours. A 6-year old was poisoned after applying a transdermal clonidine patch to their skin thinking that it was a bandage (Killian et al. 1997).

The design of safer transdermal devices has received attention in the patent literature (e.g., Cubbage et al. 1998). As an example, one approach proposes the use of a deactivating or encapsulating agent as an integral part of the device or within the device's original container into which it can be subsequently disposed (Warner et al. 2005).

Finally, a recent significant event is the guidance to industry issued by the US FDA for design of new TDDS that minimize the residual API content (USFDA (Leslie Kux) 2010). *More attention by manufacturers during TDDS design to reduce API residuals holds great potential for reducing unintended poisonings in humans, pets, and wildlife, as well as for reducing the entry of APIs to the environment.*

Leftover drugs as contributors to animal poisonings

Imprudent drug disposal also poses risks for companion animals and wildlife (particularly any animal that scavenges through trash or landfills). As with human poisonings, however, the published evidence for disposal of drugs from households as contributing to animal poisonings is thin. With this said, household pets are known to be poisoned by drugs. Pet ferrets, for example, show the ease with which pets can suffer acute poisoning by medications, especially by commonplace analgesics (Vanderlip 2009). Veterinary medications (as well as many human drugs, especially those formulated for children), are often flavored to encourage ingestion by pets. This is a common cause of poisoning in cats.

Some of the few resources that discuss companion animal poisonings by drugs include: (Berny et al. 2010; Dunayer 2004; Fitzgerald et al. 2006; Murphy 1994; Vanderlip 2009).

Compared with human pharmaceuticals, the resources for veterinarians to assist in dealing with leftover drugs is extremely limited (e.g., see: AVMA 2009; Haskell et al. 2003). While the disposal of veterinary drugs is infrequently discussed in the English literature, a formal collection system exists in Portugal (Valormed 2010).

The issues surrounding the complexities introduced to disposal from new and used delivery devices apply also to veterinary medications. The use of these devices (including transdermal systems) spans the full spectrum of animals: companion, domestic (food producing), sports, laboratory, and wild. As with human delivery devices, the concerns apply to the API residue contained in the device - as well as to the solid waste problems posed by the device itself. The array of delivery systems in use and under development are covered by Brayden et al. (2010).

Unintentional or "indirect" disposal of drugs resulting from use in veterinary practices

There are at least two ways in which drugs are used in veterinary practice that are known to sometimes serve as alternative pathways of unrecognized disposal. Certain veterinary practices involving drug use serve as indirect, unintended, hidden forms of "indirect" disposal. These practices are known to result in the most overt and significant instances of acute wildlife poisonings.

The first form of indirect disposal occurs when high-levels of drug residues remain in animal carcasses and which are then not properly disposed to prevent subsequent access by animal scavengers (e.g., shallow burial where the carcass can be easily retrieved by scavengers). Improperly disposed, drug-laced animal carcasses have been known to cause mass poisonings of wildlife, such as eagles and vultures. This phenomenon was first documented in the US when carcasses from animals euthanized with pentobarbital were improperly disposed, leading to the mass poisonings of eagles and other raptors and scavengers (USFWS 2003). In a unique study of the longevity of pentobarbital residues in buried animal carcasses, parts-per-million levels were detected in compost piles containing euthanized horse carcasses for up to a half-year (Cottle et al. 2009).

The most dramatic and well-publicized incidence of mass poisonings by drug-tainted carcasses occurred over a number of years in parts of Asia. First reported by Oaks et al. (2004), this involved cattle that had been treated with certain NSAIDs (initially diclofenac) and that soon died - leading to the mass extirpation of various vulture species that fed upon the carcasses. This led to a large-scale ecological disaster. Wildlife poisonings by drugs have been covered by: (Blanco et al. 2009; Enserink 2009; Green et al. 2004; Koenig 2006; Krueger and Krueger 2007; Lu et al. 2009; O'Rourke 2002; 2004; Rattner 2009; Shultz et al. 2004).

The second form of indirect disposal involves the use or diversion of drug-laced animal carcasses as feed for companion animals or for wildlife held in captivity. This has occurred by the use of euthanized carcasses or use of tranquilizer-darted wildlife carcasses as feed. In one report, a fatal

poisoning occurred in a captive mountain lion that was fed only a portion of a mule deer that had been darted with 10 mg of thiafentanil oxalate (a synthetic opioid anesthetic used in tranquilizer darts). Instances such as this show the susceptibility of non-target species to small amounts of certain drugs (Wolfe and Miller 2005).

There have also been sporadic and controversial reports over the years of at least the potential for euthanized carcasses to enter and contaminate the pet food chain (Martin 2002). While pentobarbital used for cattle and horse euthanasia might be the only source of pentobarbital in pet food (as verified in testing done by the FDA's Center for Veterinary Medicine, CVM), the DNA testing used by the CVM to rule out the presence of meat from euthanized dogs or cats was not able to detect contamination lower than 10% by weight (10% of the pet food mass contributed by pets) (USFDA 2001; 2002a; b). The possibility of low-level contamination by euthanized pets therefore could not be ruled out with certainty.

As a result of the FDA investigation, the FDA published a labeling change for pentobarbital used for animal euthanasia. The revised label stated in part: "Limitations. Do not use in animals intended for food."

Resources for veterinarians to assist in performing ecologically safe euthanasia and in dealing with expired drugs in general are available from the USNER (2010).

Drug disposal guidance increasing the hazard of leftover drugs

By not sufficiently considering all the hazards posed in the life cycles of drugs, guidance for drug disposal holds the potential for substantially increasing the incidence and severity of unintentional poisonings.

A substantial body of evidence shows that used patches are directly responsible for poisonings. Drug disposal programs (such as take-back or collection events) can exacerbate this problem simply by encouraging consumers to set aside their leftover drugs while waiting for sufficient quantities to accumulate - to justify making a trip to turn them in at a collection event. This behavior could result in the temporary stockpiling of extremely hazardous, leftover drugs. This could increase the potential for poisonings - simply because more types and higher quantities of drugs remain on-site than might ordinarily if disposal were performed immediately. This problem will grow worse as the development of transdermal and other deliver devices proliferates and especially as the use of highly potent APIs expands.

Efforts to ensure proper disposal might be more effectively focused on two aspects of leftover medications: (1) Acutely toxic medications (such as those in certain used delivery devices); these are medications that are known to be fatal from exposure to a single dose (e.g., in children) and are dominated by opioids. For this reason, any scenario that might increase the risk for contact should be discouraged; stockpiling waste and disposal to trash are two examples. (2) Design approaches for disposal that minimize the time during which an unwanted medication remains on-site. *The latter means that a safe disposal program needs to ensure fast removal of leftover drugs from the home or provide secure storage while leftovers accumulate prior to disposal.* Drugs that are lethal in a single dose are discussed by Daughton and Ruhoy (2009a).

The consumer cannot be relied upon to ensure secure storage. Unsecure storage occurs even with medications that are highly hazardous for children, such as methadone (Williams et al. 2009).

A specific aspect of current disposal guidance that could place consumers at increased risk is recommendations regarding pill destruction or alteration of pills to make them "unpalatable." These practices introduce new hazards that would ordinarily not be present. This is a complex and potentially very important topic, having broad ramifications for the design of drug disposal guidance. It is discussed in more detail in the sections immediately below. These potential hazards imposed as a consequence of drug disposal guidance were first comprehensively discussed in Daughton and Ruhoy (2009a, especially p 2511-2513).

Guidelines for altering, manipulating, or treating drugs prior to their disposal by consumers are ill-advised. Disposal guidelines for consumers often include steps to take prior to final disposal that entail some sort of adulteration, physical alteration, or chemical modification to the dosage form. This guidance might be directed to both solid and liquid dosage forms. The intent of these "pre-disposal" steps is motivated by any of three objectives: (i) rendering drugs unusable to others who might reclaim them (diversion), (ii) rendering drugs undesirable or unpalatable to humans or wildlife that might accidentally attempt to ingest them, or (iii) altering or degrading them for the purpose of preventing the possibility of future pollution by their leaching from the landfills.

There are a number of approaches suggested for accomplishing these objectives - and even more that consumers invent on an ad-lib basis. ***Regardless of the intent or motivation, it is highly recommended that all guidance that encourages these practices be carefully examined, as they can pose serious risks for humans, domestic pets, and wildlife.***

Some of these risks are discussed here. Most have been previously discussed in prior ORD publications, but the most comprehensive overview published to date is in several of the sections of Daughton and Ruhoy (2009a).

The risks created by pre-disposal alteration of medications derive from two major sets of liabilities of the recommended practices. The first set of liabilities results from encouraging the consumer to handle medications more than necessary or to attempt physical alteration of a dosage form. The mere act of transferring medications from their original containers poses the risk of misplacing one or more doses by spillage. Drugs spilled unnoticed onto countertops or floors can be readily picked up by toddlers and pets. This hazard is extremely high when the medication belongs to a class of drugs that can kill with a single dose (see prior section).

The transfer of medications to other containers can lead to accidental poisonings. This is a well known cause of pesticide poisonings, especially when the transfer is made to a recognizable food container. Whether the transfer is done with the intention of using the medication in the future, or whether the transfer is to another container intended for disposal, confusion results. Furthermore, once the medication is transferred, it loses its ready identity and can increase the time it takes to identify the causative agent should a poisoning occur.

Others have noted that guidance to remove medications from their original containers may be flawed (Dillon and Rubinstein 2005a, see page 26; Dillon and Rubinstein 2005b). Also, the National Association of Clean Water Agencies (NACWA) has expressed concern regarding guidance to remove pills from containers prior to disposal (Hornback 2007):

> "NACWA's final concern with the current guidelines is the recommendation to take unused prescription drugs out of their original containers. NACWA understands the reasoning for this, but for many takeback programs, the original containers and labeling are very helpful for classifying drugs and ensuring that control substances are handled properly. NACWA suggests a revision to the guidelines to ensure these drugs can be properly classified by take-back program managers."

Encouraging the consumer to physically alter a solid dosage form, such as by crushing tablets or emptying capsules, not only poses the risk of losing one or more whole doses during transfer from containers, it also poses the risk of releasing and distributing debris or dust from the crushed dosage form. Moreover, some dosage forms are specifically designed to resist crushing (unscored tablets are often not intended to be split because they are formulated for extended release), and others can become highly toxic once their normally protected contents are exposed; quite a number of oral dosage forms should not be crushed (Mitchell 2008). The consumer is unable to identify these particularly problematic dosage forms.

The potential for generation of hazardous dusts from crushing pills or from unnecessary handling is shown by studies of pharmacist exposure to particles and aerosols generated during the process of dispensing medications (Scott 2008). And dispensing is a process much better controlled than the myriad ad-hoc ways that a consumer might attempt for physically altering or destroying medications. Consumer exposure via the skin, ingestion, or inhalation of dusts generated during ad-hoc destruction has never been investigated. Inhalable dusts are of particular concern for APIs known to sometimes elicit strong immune responses, such as penicillin.

The dangers posed by crushing are shown in the publications primarily from the nursing literature (e.g., Paradiso et al. 2002; Stubbs et al. 2008). Tablet crushing and capsule opening are standard (but under-reported) practices in geriatric nursing. It is a practice known as "dose modification" and is used in healthcare (often unwisely) in attempts to make it easier for patients having trouble swallowing their medication. Even when performed by experienced personnel using proper equipment for crushing, the practice is viewed as one with noted risks - especially with enhanced toxicity of the dose form (a particular concern with APIs having narrow therapeutic indices).

Even if a drug is scored, indicating that it is also possibly crushable, this does not mean that it would be safe to crush. Extended release dosage forms, for example, should not be crushed, as their higher API content can be acutely toxic, especially to children and pets. While dose modification may not result in severe adverse effects for those who have already been adapted to a medication, for those who are naive to the subject API, the consequences from ingestion of modified doses can be lethal; this is particularly true for opiate ingestion by those who are opiate naive.

For the consumer, an additional likelihood is crushing multiple different types of medications together, as drug-drug interactions could result from exposure to dispersed residues. Certain

enteric-coated medications, when crushed, can act as severe esophageal irritants. Crushing of extended release formulations is particularly hazardous for ingestion, as it promotes the rapid release and absorption of API to levels that far exceed therapeutic levels. The dose that was designed to be released over an extended period of time is released all at once. Some mortalities have been reported from overdoses resulting from what would normally have been safe doses if the dosage form had not been altered. Many drugs come in extended dose forms, examples being aminophylline, diltiazem, and morphine. The potential for spillage and loss of crushed drugs during crushing or capsule opening are real. Even among experienced nurses, unnoticed spillage and loss have been observed (Stubbs et al. 2008).

Some drugs contain APIs that are extremely hazardous even under normal usage. They are coated to prevent dermal exposure by the handler or during administration. Some should not be handled by certain sub-populations (e.g., pregnant women handling teratogens, such as: tamoxifen, methotrexate, and finasteride). Crushing can not only enhance dermal exposure, it can also create an exposure pathway that would ordinarily never otherwise exist - for example, pulmonary exposure via inhalation of dusts or particulates from oral dosage forms.

These two hazards (enhanced absorption of toxic doses and new exposure pathways) as a result of pill crushing prior to disposal were first pointed out by Daughton and Ruhoy (2009a).

Sometimes adulterants are recommended in disposal protocols, such as the addition of diesel fuel, which only serve to add to the overall environmental hazard once they enter landfills. Another suggestion to consumers is to add water to medications prior to disposal. Many medications will not readily dissolve in water, making them easy to reclaim. For those drugs that will dissolve, a new hazard is created from the potential for leakage from the containers. This can result in spillage of concentrated API anywhere along the route traveled by trash. It also increases the potential for APIs to enter landfill leachate.

With these issues aside, since the major intent from all of these operations is simply to make the drugs undesirable or unpalatable, this is not sufficient to discourage those who are determined to reclaim a particular drug - - as a truly motivated abuser or addict can always re-purify a drug from just about any type of mixture. This is best shown by the great efforts expended by desperate meth addicts. Law enforcement periodically comes upon a type of clandestine lab operation called a “urine extraction lab” or “pee lab,” where methamphetamine that has been excreted unchanged in urine or feces is reclaimed with the use of chemical extraction; those engaged in this activity are called “tinkle tweakers.” Others, termed “dirt barons,” are known to revisit the sites of abandoned clan labs and attempt to extract residues from dirt and discarded waste (FACT 2006; Majors 2009).

Some of the limitations and potential hazards posed by disposal guidance can be observed in any of the numerous videos posted on the web that discuss drug disposal or take backs. A video showing the disposal protocol recommended by SMARxT (2008) serves as a representative example. From this video, several observations can be readily made. First, there are multiple steps involved in the recommended protocol. Not only is this a time-consuming task - one that many consumers would likely not follow - but moreover, most of the steps impose new hazards. For example, the plastic bag could be easily pierced or ruptured, spilling dry or wet contents on

countertops or floors. Second, it inadvertently encourages improvisation by the consumer when all of the needed materials (freezer bags, cat litter, coffee grounds, etc) are not readily available. Also shown is the removal of container labels. While this may or may not be prudent (e.g., it makes future identification of the disposed medication much more difficult, should an accidental poisoning occur), it is not always feasible, as some labels are nearly impossible to remove from containers because of the adhesive used. Note that the use of cat litter for drug disposal dates back to at least 1996, but for a different purpose. Its use was originally evaluated to facilitate the disposal of small amounts of leftover liquids - particularly anesthetics - not for the still unproven purpose of discouraging the recovery of disposed drugs (Tarling et al. 1996). EPA's study of best control practices in the healthcare industry for unused medications also cites disposal of controlled substances by crushing and mixing with kitty litter (Lucy and Wu 2009).

The second set of liabilities results from suggestions to chemically modify medications in order to render them unusable or more innocuous for the environment. There are uncharacterized hazards with rendering drugs unusable by chemical alteration. If reactive chemicals (e.g., oxidants such as chlorine) are used to denature the drugs, the release of hazardous, volatile by-products might result. Some consumers might be tempted to employ hazardous reactants such as concentrated acids or bases - or even to apply heat such as with an oven or heat gun.

Here is an example of State disposal guidance where new, untested practices were introduced (New Mexico Board of Pharmacy 2010): "Add water with bleach to container until contents are completely covered." Bleach could react with amino functionalities common to many APIs, creating toxic and volatile chloramines. Hypochlorite could also possibly react with APIs to create a plethora of halogenated by-products.

With regard to chemical alteration, it is often suggested that rigorous chemical treatment might serve as a replacement for incineration (such as for disposal of controlled substances). The research that has been performed on chemical destruction of drugs has focused on genotoxic and mutagenic drugs such as antineoplastics (as a means of occupational control). No single form of treatment, however, has proved effective for all APIs, and many of the reactants used in these studies are hazardous to handle themselves. The discussion that follows summarizes a few of the many studies that have relevance to this aspect of drug disposal. *In the final analysis, no simple, safe, rapid, and green method exists for rendering unwanted medications unusable and unrecoverable.*

Pre-treatment of drugs prior to disposal by healthcare facilities and pharmacies. The types of medications requiring disposal by healthcare facilities and pharmacies can differ dramatically from those commonly stocked by households. Many are highly hazardous, such as antineoplastics. For this reason, considerable research has been targeted at occupational exposure, especially regarding ways to decontaminate or to destroy leftovers. Some of the published results are also relevant to consumer disposal - pointing to the many problems that could be encountered by the consumer who attempts to destroy medications.

The application of heat is often considered by consumers. Autoclaving and microwaving are technologies used by healthcare facilities for destroying pathogens - for disinfection or sterilization. By heating with pressurized steam for a half hour (at temperatures over 140°C),

infectious agents are efficiently destroyed by autoclaving. They are not intended for destroying chemicals. These technologies impart very low energies compared with incineration.

Certain drugs, most notably antineoplastics (e.g., oncolytics), can and will accidentally or intentionally become mixed in with healthcare wastes (Armstrong and Reinhardt 2010); examples are residues on soiled textiles and in syringes. They also become dispersed around preparation areas and areas where treated patients stay, creating the need to minimize occupational exposure after preparation of infusions and handling of patient wastes. There is therefore great interest in having adequate decontamination protocols. These have been the primary drivers for research on drug destruction.

Antineoplastics (and residual mutagenicity) have been shown to persist in urine stored for several weeks (Monteith et al. 1987). Oxidation with sodium hypochlorite or potassium permanganate is often the most successful treatment (as opposed to hydrogen peroxide), but no approach has been shown 100% effective at stoichiometric destruction of both the parent API and reaction by-products - as well as at avoiding the generation of mutagenic by-products. Much of this work was initiated by the International Agency for Research on Cancer (IARC) (Castegnaro et al. 1985).

A number of studies have examined the chemical degradation of a variety of antineoplastics: (Barek et al. 1998; Benvenuto et al. 1993; Hansel et al. 1997; Lunn et al. 1989; Monteith et al. 1987; Roberts et al. 2006). A summary of drugs for which larger-scale chemical destruction methods have been developed is provided by Prüss et al. (1999, see page 117). An important feature that can be distilled from these studies is that not all antineoplastics can be effectively destroyed by a single reactant or under the same physical conditions. Multiple reactants and compositions would be required for rigorous destruction to innocuous mineral products.

NIOSH has compiled an extensive list of references that focus on antineoplastics in the occupational setting (NIOSH 2010). The sections that have relevance to drug disposal are: (i) Effects of Occupational Exposure, (ii) Environmental Sampling, and (iii) Decontamination and Deactivation of Antineoplastic Agents.

Some studies have been done to determine the fate of antineoplastics in autoclaves. One study (Bassi and Moretton 2003) investigated the mutagenicity of solutions of various antineoplastics before and after autoclaving: cisplatin, carboplatin, doxorubicin, 5-fluorouracil, methotrexate, and cyclophosphamide. Mutagenicity was not altered for doxorubicin, 5-fluorouracil, cisplatin, and carboplatin. But it actually increased 5-fold for cyclophosphamide, presumably because of the formation of mutagenic hydrolysis products.

Photolysis using a medium-pressure mercury lamp was also investigated as an effective means for completely destroying a variety of APIs at high aqueous concentrations (grams per liter), Some APIs required the presence of hydrogen peroxide; no mutagenic by-products were detected (Lunn et al. 1994).

One approach to physical destruction has the potential to release significant dust or fine particles - the use of shredders or disintegrators. These can pose very real hazards especially to those who

operate the machinery. Perhaps the most telling evidence that should highlight the potential hazard is the work published on the preparation of cytotoxics and other chemotherapeutants. Even the use of stringent containment protocols during the preparation of chemotherapeutics does not prevent their escape into unconfined areas or the inhalation of vapors (Daughton and Ruhoy 2009a). Further, crushed medications might also pose a greater hazard in landfills with regard to leaching and exposure of wildlife.

Occupational hazards of drug waste and relevance to consumers. The one class of drugs that probably demands the most attention regarding their use and disposal is the antineoplastics. This class is diverse and comprises highly toxic mutagens and carcinogens. Cytotoxics are documented contaminants of surfaces in healthcare settings. This problem has been summarized by Daughton and Ruhoy (2009a). Contributions come from both the healthcare provider and from treated patients. Even the standard use of the needle/syringe technique when withdrawing highly toxic antineoplastics from their containers has been shown to contaminate the immediate surroundings (Spivey and Connor 2003). Antineoplastics can also vaporize from spilled solutions or contaminated liquids (Connor et al. 2000).

The potential for occupational exposure during preparation, administration, and waste management are well known. Many are volatile and can readily contaminate surfaces in the vicinity of their usage. An emerging concern is whether development of various cancers is a widespread occurrence for those involved with continual occupational exposure to antineoplastics (Smith 2010).

While these phenomena pose obvious occupational risks, by extension they also have ramifications in the homecare setting. Originally confined to use only in hospitals and infusion clinics, the use of hazardous drugs has been expanding, driven somewhat by off-label use (such as treatment of various rheumatic diseases and multiple sclerosis) and also by use in physician offices (ASSTSAS 2008). They are also experiencing growing veterinary use.

Most reported cases of occupational poisonings have involved steroid hormones and cytotoxic anti-cancer drugs. Pulmonary exposure to dusts and particulates are a major problem, although contact reactions, such as sensitization, from dermal exposure also are known to occur. These instances all point to the potential risks that may be associated with recommending that consumers "crush" their medication prior to disposal. Many new APIs are being designed with much greater potency, with some having occupational pulmonary exposure limits below a microgram per cubic meter (Cherrie et al. 2009; Heron and Pickering 2003).

Despite the extreme hazards associated with these chemicals, regulations for their safe use in occupational settings are not set forth by OSHA, which only provides guidance and information for occupational use of antineoplastics (OSHA 1996; Polovich 2004). Voluntary guidelines for those who work with antineoplastics are issued by NIOSH (2004).

While occupational exposure and disposal is not the focus of this report, the expanding use of antineoplastics in the home setting and in veterinary clinics does pose concern. The potential for exposure is not limited to just the administration stage, but also the handling of patient (and animal) waste (excrement and clothing) as well as leftover drug waste. Even interdermal transfer

from those under treatment to others is possible (Daughton and Ruhoy 2009a). Unintended exposure to ambient levels of antineoplastics for those not undergoing treatment has been termed "secondhand chemo" in the popular media (Smith 2010).

The growing use of highly potent APIs (HPAPIs) will require the development of new dosage forms, simply because of the difficulty in ensuring that each solid dose (which have convenient weights of about 200 mg) contains such a small mass of API (e.g., a microgram). This problem is being addressed with new approaches, such as the use of inkjet printing for making "printable pills," where the dose of a highly potent API is printed on the surface of a conventionally sized tablet that can be easily handled by the consumer (Canavan 2010).

Pre-treatment of leftover drugs prior to disposal by collection events. Some local collection events have sought to independently solve the limitation of not being able to accept the return of controlled substances by attempting to render the dosage forms unusable on-site (a practice that the DEA does not permit). This practice has usually involved schemes to dissolve the drugs in bulk containers containing acidified water. The problem is that the constituent APIs are merely dissolved in an aqueous solution. They are not structurally destroyed as required by the CSA.

On-site destruction has been tried, for example, in collection events in Florida (Musson et al. 2007). Some excerpts from this report reveal the inadequacies of the approach:

> "It was desired that the unwanted medications became no longer recognizable and unusable when deposited into the container. It was determined through experimentation that a mild hydrochloric acid solution (1 mL of 20 Baume HCl to 12 L of water) with a pH of 2.0 was capable of dissolving the pharmaceuticals and rendering them unusable. This acidic solution was used in collection containers at all of the locations except one location." … "Although the vast majority of the pharmaceuticals were disintegrated by the collection solution, some partially decomposed medications were observed. In addition, during emptying of the collection containers, it was observed that several medications remained in their tamper-proof packaging, having not been removed by the participants during their disposal."

Another consideration regarding collection approaches that combine all medications into single containers for chemical treatment pose chemical incompatibility concerns.

Pre-treatment of drugs by encapsulation prior to disposal. As an alternative to attempts at chemical alteration of drugs prior to their disposal, an approach used by pharmacists in the UK for many years has involved kits that serve to encapsulate drugs in small batches, purportedly permitting safer disposal in landfills and preventing diversion. These are often referred to as DOOP (Disposal of Old Pharmaceuticals) Kits. Encapsulation using these kits has never been evaluated for long-term effectiveness in providing a sustainable solution. In the US, similar kits have become available for consumer use (F.P.R. Inc. 2010; Parrott 2010; Rx Disposal Solutions 2010).

But all of these kits are surrounded by the same unknowns regarding the potential for leachability, as well as the many concerns highlighted above with regard to encouraging consumers to physically handle drugs more than necessary.

Take-Backs; DUMP, DOOP, and RUM campaigns; home and hospital inventories

The en masse collection of unused, leftover medications is a hazard-reduction practice that has been underway for roughly 50 years - since the 1960s and perhaps earlier. The DDS database contains over 100 articles on various types of drug collection activities and on obtaining data on drugs inventoried during collection events and in the home. One of the first published collection events for drug waste was Nicholson (1967), who was also among the first to publish an inventory of returned drugs - not just the quantities, but also the identities. Over 43,000 tablets were collected, and over 36,000 were identified. But the first major study to inventory medications that were naturally returned to a pharmacy was Hawksworth et al. (1996), who provided data more representative of the public as it was done without any of the formal advertising used in attracting attention to collection campaigns. Their study was also among the first to study the reasons for returns.

Since the seminal reports up through the 1970s, a wide array of approaches have been attempted for collecting unwanted drugs - ranging from simple one-time local events to ongoing formal programs that span larger geographic regions. Depending on the country, approaches have ranged from consumers transporting their returns to pharmacies or collection sites, or, most recently, the use of the mail (in the US). Although most collection activities have been targeted at consumer drugs, some have targeted healthcare facilities such as hospitals. Many of these efforts were formal studies with intents on collecting data, but perhaps even more were done simply as a public service to rid homes of leftover medications. Motivations for the former have included the use of leftover drug data to study patient non-compliance or the monetary value of the wasted pharmaceuticals (to see where savings could be made in the prescribing and dispensing processes). Motivations for the latter have primarily been to reduce the potential for drug diversion, drug abuse, accidental misuse, and unintentional poisonings.

The collection of leftover drugs has taken place under a variety of names, depending on the country. The first formal collection events targeted at consumers began in Britain in the 1970s and were called DUMP campaigns - Disposal of Unused Medicines and Pills - a term possibly coined in a 1975 Manchester study (Bradley and Williams 1975). But since the acronym DUMP had negative connotations (sometimes being misunderstood for random dumping), alternative names were soon employed, such as Medidrop. An overview of the UK's DUMP campaigns is presented by Forbes et al. (1989).

Mackridge (2005), however, points out that the origin of the DUMP acronym is ambiguous, as it has been translated with a variety of meanings: Disposal of Unwanted Medicines and Pharmaceuticals; Dispose Unwanted Medicines Properly; Disposal of Unwanted Medicines and Pills; and Disposal of Unwanted Medicines and Poisons.

One of the largest and oldest take-back programs is RUM (Returning Unwanted Medicine), whose collections have been averaging around 400 tonnes (400,000 kg) per year (Brushin 2005; RUM 2008). Brushin (2005) provides a detailed examination of the RUM program. An overview of the returns programs in Canada is provided by Gagnon (2008; 2009).

In British Columbia, Canada, the Medications Return Program (MRP, launched in 2001) was formerly the Post-Consumer Pharmaceutical Stewardship Association (PCPSA). All manufacturers of prescription and OTC medications are required to take responsibility for the safe disposition of leftover medications (Driedger 2002). Reports from the BC MRP provide examples of the types and magnitude of data collected from returned drugs. During a 1-year period (2005), over 18,000 kg (18 tonnes) of medications were collected (PCPSA 2006). For the year 2007, the total collected had increased to 23,875 kg (Vanasse 2008). And for the year 2008, the total collected had again increased, to 35,704 kg (Vanasse 2009). The usefulness of the collection data from the MRP is also similar to that of other programs. It is important to recognize that the data do not specify what exactly had been measured - the drugs by themselves or also packaging; the data most certainly do not pertain to the mass of collected API.

France conducts pharmacy-based collections under the MNU program (Médicaments Non Utilisés: medicines not used). One such program is the Cyclamed program, implemented in 1993 and funded by the pharmaceutical industry; Cyclamed, however, does not accept return of OTC or veterinary medications (Cyclamed 2008).

A number of other acronyms and terms are sometimes used for drug collections. Take-back services provided by pharmacies in the UK and Wales use the term DOOP service: Disposal of Old Pharmaceuticals. Collection programs are sometimes referred to as "drug amnesty" programs, especially when illicit drugs can be included in the returns.

Summaries of some of the formal programs and organizations in other countries that collect returned drugs are provided by the Northwest Product Stewardship Council (NWPSC 2008) and by CalRecyle (CalRecycle 2010c).

Note that Federal laws and regulations have played a major role in the shaping and constraining of approaches available for collecting unwanted medications in the US. This is the major reason that the challenges in the US differ from those of other countries. The uneven patchwork of take-back events and programs in the US is a result of an absence of national guidelines and differences among local and state laws and regulations. As one of many examples, commonly understood is that law enforcement needs to be present if controlled substances are going to be accepted at a take-back event. Some states, however, require the presence of law enforcement regardless, probably to prevent diversion of controlled substances that consumers inevitably attempt to turn in; some have different requirements for additional agencies to be involved with collection of controlled substances.

Various guidances from state and federal agencies for consumer drug disposal are compiled or discussed by PSI (PSI 2009). CalRecycle has summarized international and other state programs (CalRecycle 2010b). Many listings of take-back efforts are provided by individual states; a few web sites provide compiled listings for the US (Illinois-Indiana Sea Grant -Year Unknown; NADDI 2010; PSI 2008b; Teleosis Institute 2010).

One of the most concerted efforts to date to develop statewide model programs for collection of unwanted drugs from consumers for proper disposal is the effort by the California Integrated Waste Management Board (CIWMB), which was mandated by state legislation (CalRecycle

2010a; Simitian and Kuehl 2007). Texas has implemented a similar workgroup under the TCEQ - the Pharmaceutical Disposal Advisory Group, which was convened to obtain information required by Texas SB 1757 (TCEQ 2010).

The continually growing popularity of take-backs is shown by the entry of commercial interests into the consumer take-back sector. The TakeAway(tm) program of Sharps Compliance, Inc., is one example (Sharps Compliance 2010a).

Drug collection programs have been the central focus of nearly all efforts to reduce the entry of APIs into the environment, despite there being little evidence that their impact would be measurable. Although some obvious measures are possible (such as calls to poison control centers, drug arrests for prescription drugs, confiscations in schools), few attempts have been made to link possible trends to collections. The primary impetus is believed to be that drug disposal is the most obvious aspect of the drug life cycle that can be easily and directly controlled by the public. As seen in the many other sections of this report, however, there are numerous other points of attacking the drug life cycle that would have much greater pay-offs in reducing the presence of APIs in the environment.

With this aside, the real value in drug collection activities would potentially derive from key data that could be mined - data that could be used for assessing, designing, and implementing other approaches for up-stream pollution prevention. But these data must be collected by way of detailed inventories of the collected drugs. Taking inventory of returned drugs is extremely time-consuming, requires pharmacy experts, and incurs substantial costs. No evidence exists that these costs could be justified on the basis of reducing down-stream impacts - that is, for removing an unknown and possibly low percentage of drug residues from the environment. But the type of data that can be mined from returned drugs could hold extraordinary central importance with regard to solving the up-stream activities, actions, and behaviors that lead to API entry to the environment in the first place. Examples include identifying which drugs are over-prescribed or that elicit poor patient compliance so that adjustments in the prescribing system can be made, resulting in fewer wasted medications or in fewer medications used (thereby also reducing excretion).

One potential use of drug-returns data has never been capitalized on. Those drugs captured by inventories most frequently or in the greatest quantities could be used to better inform or prioritize the selection of APIs to target for environmental monitoring. One example of this is in James et al. (2009).

The EPA has been working toward covering hazardous pharmaceutical waste under the Universal Waste Rule (40 CFR, part 273). The intent has been to facilitate the collection and disposal of drugs as hazardous waste. The UWR applied to drug waste would essentially allow a facility to act as a “handler” of pharmaceutical universal waste instead of having to abide by the more onerous requirements imposed generators of hazardous drug waste. This may simplify and reduce the cost of handling waste collected from public take-backs (USEPA 2010a). Moreover, this change would allow nonhazardous pharmaceutical waste to also be treated as Universal Waste, helping to divert these products from municipal waste streams. This modification to the rule, however, has not been without debate (e.g., NACWA 2009a).

Mail-backs. The approach used in nearly all collections activities is physical transport by the consumer to the drop-off site. This approach incurs added costs from transportation and consumer time, and requires planning ahead. Some consumers are unable to conveniently travel and many locales do not have access to collection sites. Most importantly, the use of episodic take-back events encourages and perpetuates one of the major consumer behaviors long-sought for elimination by drug-control programs - episodic take-backs force the consumer to amass and store leftover medications - a practice that imposes the same risks for diversion and unintended poisonings as does hoarding.

One of the only approaches explored beyond the drop-off paradigm is the use of the mail system. The use of mailers ("mail-backs") addresses many of the shortcomings of drop-offs. Its major advantages are that it is always conveniently available, and, moreover, it does not encourage stockpiling while awaiting a take-back event. One of the little-mentioned aspects of physical, on-site take-back campaigns is that the public is known to sometimes resort to prior practices (e.g., disposal to trash and sewers) as soon as the campaigns cease (Gill and Portlock 1990).

The State of Maine pioneered the mail-back approach with the “Safe Medicine Disposal for ME” (SMDME) program. The SMDME is a statewide program established through state legislation. It was first implemented in 2007 with a grant from the EPA's Aging Initiative. The program is innovative in that it uses return mailers and can legally accommodate all medications - including controlled substances and illegal drugs, should the consumer decide to include these types of drugs. During its pilot stage, a major objective of the program was to catalog returned medications. Maine is the first state to seek statewide solutions to drug disposal. It passed the first proclamation in the nation on safe drug disposal to be endorsed by a governor (State of Maine 2003). Kaye et al. (2010) provide a comprehensive report on the Maine SMDME program. Some other discussions of Maine's mail-back program are provided by Crittenden and Gressitt (2009) and Kaye (2008).

Some of the findings from the inventories performed by the SMDME program comport with those noted by others. These include the receipt of drugs that span the spectrum of time held. Some returned items were full containers of medications (many from mail-order pharmacies or U.S. Department of Veterans Affairs [VA] pharmacy services, and some of which are quite costly, such as antiretrovirals), while others were decades old. Some patients received the same medication from different pharmacies (e.g., both mail-order and local). The monetary value of narcotics received from some individuals had street values of thousands of dollars, representing significant targets for diversion.

The major potential criticism of the mail-back approach is the risk of diversion. Although instances of diversion of drugs en route from mail-order pharmacies has been documented, a comparative risk analysis has not been done versus the alternative of continued storage in the home or for physical take-backs. From its collaboration with the State of Maine, the USPS announced on 8 April 2010 that it would be piloting an expansion of mail-back programs by offering the service to the U.S. Department of Veterans Affairs (VA) in Washington, DC and vicinity (USPS 2010).

Role of the CSA. A unique aspect of the still-evolving approaches to drug disposal in the US is the Controlled Substances Act (CSA) (US Department of Justice 1997). The CSA imposes challenges and obstacles to the development of a straightforward, sustainable approach to drug disposal, as it prevents the transfer of controlled substances from the patient who was issued the prescription to any other entity except those few stipulated in the CSA. Among those excluded from being able to accept the return of controlled substances are healthcare professionals and pharmacists.

The CSA also impacts nursing homes and long-term care facilities (LTCFs), which inherit unused controlled substances no longer needed by patients, such as in the event of death. The CSA does not allow these facilities to transfer these controlled substances to others for disposal. This is the origin of witnessed disposal to sewers at these facilities.

The CSA as it pertains to dispensing and disposal of undispensed controlled substances by pharmacists is explained by the DEA (Ashcroft et al. 2004). A summary of the complexities and nuances surrounding the CSA and the disposal of controlled substances is available from Vivian (2009). An overview of the complexities, intricacies, and impacts of the CSA with respect to dispensing is provided by (Van Dusen 2010).

The DEA has prepared two documents to assist those who handle drugs with understanding the Controlled Substances Act and its implementation (Bonner and Haislip 1991; Rannazzisi and Caverly 2006).

Much of the newly proposed federal legislation directed at improving the drug disposal process in the US relies on changes to the CSA (e.g., H.R.1359, and its companion measures, S.1292 and S.3397) (Klobuchar et al. 2010; Klobuchar et al. 2009; Stupak and Smith 2009). Discussion of the CSA with respect to new federal legislation is available from Yeh (2010).

Other countries have laws governing other lists of controlled substances, but these laws have not impacted the collection of leftover drugs as has the CSA. For example, the UK's specific legislation for the handling and administration of drugs with abuse potential (referred to as "controlled drugs") is regulated by the Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 1985 (updated in 2001).

One of the ironies of the impact of the CSA on drug collections is the difficulty in obtaining data on unwanted controlled substances via drug collections. Of considerable interest is better understanding the overall contributions of controlled substances to drugs collected in take-backs. The overall percentage of total drugs that comprise legal controlled substances in households is unknown. The limited data gathered from drug collection events is not sufficiently comprehensive to draw firm conclusions. Many reports simply repeat the figures that 5-15% of all drugs collected at take-back events are controlled substances. But some real-world data report up to one-half as being controlled substances (Bay Area Pollution Prevention Group 2006). The report from the EPA-funded Maine pilot program contains data on controlled substances (Schedules II-IV), where they represented roughly 17% of the total number of pills collected in a mail-back program (Kaye et al. 2010). One of the only studies to focus on the return of controlled substances and drugs of abuse (to pharmacies) is Mackridge et al. (2007). A study in

Sweden showed a much lower return rate for controlled substances compared with other drugs. The authors speculated that these drugs were preferentially hoarded or diverted for non-medical use (Ehrling 2005).

Role of expiry and shelf-life

Drug expiry is a major factor at play in a number of aspects of the larger drug disposal issue, including generation of leftovers, maintenance of drug stockpiles for national security and national healthcare, imprudent humanitarian donations, drug reuse/recycling, purported toxicity (e.g., from formation of impurities), counterfeiting, and stewardship.

Much confusion surrounds expiry. Comparatively little effort has been invested in trying to determine the actual expiration of drugs and in developing ways to extend it. This is largely because of the extreme difficulty and complexities in developing meaningful test criteria. This has profound implications not just for the cost of healthcare (premature drug wastage), but also for environmental impact (accelerated disposal). Much of what is known from actual data has been made available from three major sources: (1) accelerated "stress testing" done by manufacturers (e.g., Carstensen and Rhodes 2000; Ju and Chow 1996), (2) real-world shelf-life testing done by the military to control costs (e.g., Rundstedt 1993), and (3) small studies by independent investigators (data derived primarily from assay of drugs long past expiration).

A summary of the expiry issue is available from the American Medical Association (AMA 2001; Okeke et al. 2000).

Complicating the debate even further (especially with the intent of legislation) is the use of multiple terminologies. Sometimes used interchangeably, these terms refer to different aspects of drug use and shelf-life. These include expiration date, discard date, and beyond-use date. The expiration date is set by the manufacturer in accordance with guidelines set by the FDA and USP.

Shelf-life is set by the manufacturer as the maximum time they guarantee acceptability (generally over 90% potency). Discard or beyond-use dates are set by a dispensing pharmacist, but cannot exceed the manufacturer's expiration date. Because dispensing medications often involves breaching the integrity of the factory container, the dispensed drug can be exposed to more onerous conditions (such as excessive humidity or microbial contamination), accelerating the degradation of the API. The discard date therefore can commonly be sooner than the expiration date. While consumers find this frustrating or uncalled for, and some states have at times mistakenly regarded it as a fraudulent pharmacy practice, no suitable means has been developed to quickly determine the potency of a medication; a test would have to be applicable to all APIs and all formulations - an impossible requirement to meet with current technology. Some effort has been devoted to developing more generic approaches to stress testing (Klick et al. 2005). In silico approaches to predict degradation are under development (Lhasa Limited Leeds UK 2009).

Expiration of valuable stores of critical medicines in developing countries is often perceived to be caused in large part by the fact that many of the supplies have been donated, causing problems

and confusion with regard to inventory of excessive numbers of medications. Some of the major causes for expiration of medications in inventories maintained by healthcare providers and pharmacies are provided by Nakyanzi et al. (2010). Many of these causes point to the need for implementing just-in-time supply practices (Daughton and Ruhoy 2010).

The US FDA's required stability testing determines whether a drug can maintain its chemical identity, strength (potency), purity, and overall quality over the duration of time that the manufacturer stipulates for the stated shelf-life (via an expiration date); note that the guidelines pertain to drugs with single APIs and therefore cannot account for the possibility of interactions between multiple APIs (in combination dosage forms). Manufacturers establish expiration dates by rigorous testing procedures called "stress testing" that attempt to emulate adverse storage and usage conditions that might be commonly experienced under real-world conditions. In reality, shelf-life is an extremely complex function of numerous interacting and wildly changing variables. Some of the variables that should be considered are heat, cold, range and rate of change in temperature, humidity, light, type of container, frequency of container openings, interaction of APIs with other chemicals, dosage form (e.g., solid versus liquid), and how all of these interact.

For these reasons, expiration dates (or discard dates) do not necessarily mean that a medication cannot remain useable for longer periods. Indeed, stability has been noted for some medications for periods of 10-15 years or more; this is especially true for solid dosage forms. But note that two of the factors most affecting shelf-life are humidity and temperature, and these tend to be maximized in the two locations of a home most used for medication storage (i.e., the kitchen and bathroom).

There are so many factors involved with drug stability that it is simply not possible to accommodate them all in stability testing. The results from stability tests therefore prompt many questions with regard to their predictive value under real-world conditions. One of just many examples showing the nuanced complexity is the difference between the removal of a container's plastic cap during testing versus removal under actual usage by the consumer. The variables become innumerable when considering the types of plastic caps and containers, types of closer mechanisms, swings in temperature and humidity, and patient misuse or abuse of the container (Shabir 2008). These problems are compounded with the introduction of ever-more diverse and complex containers and delivery devices.

Concerns are not just loss of potency (from the physicochemical breakdown of the formulated API), but also formation of hazardous reaction products, failure of the formulation (e.g., reduced propensity of a tablet to dissolve; precipitation of API from solution), or growth of bacteria (e.g., from breakdown of the preservative). One criticism of accelerated stress testing is the use of conditions that are unrealistically harsh, leading to the formation of "irrelevant" or unrealistic degradation products or degradation-related impurities (DRIs) (Klick et al. 2005).

Long debated is whether a better understanding of shelf-life and ways to ensure optimal storage conditions could extend expiry, possibly leading to fewer leftovers. The published literature is replete with debates as to whether drugs really expire and arguments that better knowledge of expiry could reduce the incidence of disposal.

Loss of potency is perhaps the major concern with regard to use of expired medications. But also frequently cited is the potential for increased toxicity. The published literature (e.g., Anon 2002), however, does not support a focus on increased toxicity: "There are virtually no reports of toxicity from degradation products of outdated drugs."

Human toxicity resulting from expired medications is a notion that originated with a single report (in 1963) regarding degradation of tetracycline; but even this report has been called into question (Pharmacist's Letter/Prescriber's Letter 2007). Even so, isolated reports sporadically surface of new concerns, as illustrated by gabapentin degrading to 2-aza-spiro[4.5]decan-2-one (gabapentin lactam), an DRI with demonstrated toxicity (Khan 2010).

A major program that has contributed much to the understanding of shelf-life is the DoD/FDA SLEP program (Shelf-Life Extension Program), the largest and longest-running drug shelf-life evaluation study. Many insights have emerged from this extremely useful program, which has also served to save millions of dollars by allowing the military to delay its stockpiled drug replacement schedules. The SLEP program has established that when properly stored, many drugs can be used for periods extending substantially past their expirations - e.g., an average extension of 66 months for 88% of the tested lots (Courtney et al. 2009; Lyon et al. 2006).

While real-world shelf-life might sometimes be much longer than stated (when stored under optimal conditions), the range in shelf-life can vary markedly among production lots (Khan 2009).

Another program, the Strategic National Stockpile (SNS) monitors drug potency, but not past expiry (OPHPR 2010).

The SLEP has demonstrated that expiration dates are extremely conservative for optimal storage conditions, with many drugs maintaining over 90% of their API content for years longer. And given the very large cost savings demonstrated by the SLEP (Woods 2005), many have found it surprising that (with one recent exception) no analogous programs have been attempted for drugs in the consumer domain. This is even more surprising given that the American Medical Association made this recommendation nearly a decade ago (AMA 2001). An example of a recent attempt at organizing some limited independent testing on a select number of drugs is the program designed by the Prescription Research Institute (Prescription Research Institute 2010).

Many reports of shelf-lives that considerably exceed expiration lend controversy to the expiry issue. An overview is presented by Lyon et al. (2006). Some specific examples include the following. A number of drugs have been shown to have shelf-lives of 9 years and beyond those stated (Stark et al. 1997). Amantadine and rimantadine hydrochloride (anti-influenza A) have been found to be extraordinarily stable under ambient conditions for over 25 years - with no loss in potency (Scholtissek and Webster 1998). Theophylline has been shown to retain 80% of its potency more than 30 years after being stored under household conditions (Regenthal et al. 2002). Metoprolol and propranolol, when stored under routine conditions, had shelf-lives of at least 5 years (Jasińska et al. 2009a; b). Even drugs that are the least stable, such as those requiring refrigeration, are known to maintain potency past expiration. Of the roughly 200 or so

drugs that require refrigeration, many are known to be stable at room temperature for days, months, or years (Cohen et al. 2007). Some drugs have been shown to maintain stability even under tropical conditions (Bate et al. 2009).

While much attention has been devoted to the fact that many medications can retain potency past their stated expiration dates, much less attention has been devoted to the incidence of drugs rapidly declining in potency prior to their expiration dates because of the adverse conditions of their storage. This might be particularly true for medications requiring refrigeration or those particularly susceptible to light, heat, freezing, or humidity. Known examples are rare, and include: epinephrine (dark storage required; must also minimize oxidation by air), carbamazepine (in tablet form reported failure to dissolve), and notably nitroglycerin, insulin and some liquid antibiotics. It is important to recognize that drugs can be adversely affected not just by excessive heat, but also by extreme cold. Freezing, for example, can alter the formulation of a drug, changing the absorption characteristics of the API; this is a particular issue for liquid formulations, where APIs can precipitate (Shea et al. 1981).

At this other end of the shelf-life spectrum are drugs stored under non-optimal conditions by emergency medicine services, such as ambulances. These may degrade prior to expiration (Fowler -Year Unknown; Gammon et al. 2008). Some stability studies targeted for the potentially extreme environments of ambulances, however, sometimes show that certain medications are extremely stable. One example is diazepam gel, which was shown to be suitable for 48 months (Alldredge et al. 2002).

One aspect of shelf-life rarely mentioned is the possible role of microbial contamination in serving to degrade the preparation (Baird et al. 1979).

Illustrating several of the countless factors that complicate prediction of shelf-lives are the following. Pharmacy compounding makes determination of shelf-life much more complex, especially for reactive APIs such as chemotherapeutics, which can have shelf-lives of hours (Benizri et al. 2009). With medications having more than one API, if two or more APIs are deliquescent, the relative humidity required for the solid-solution transition is lowered. This leads to API dissolution at humidities lower than ordinarily expected. Once in solution, APIs that are more reactive chemically can degrade faster (Mauer and Taylor 2010).

Finally worth noting is that expired drugs can serve as a source for counterfeit drugs, simply by their relabeling with new expiration dates and reintroducing them to the distribution system (Hileman 2003).

Roles of packaging and medication devices

Drug packaging can play significant but little-discussed roles in drug waste. The design of drug packaging, including containers and delivery devices, can: (i) serve as a waste problem itself, separate from that of the actual drug, (ii) amplify the generation of leftovers and the subsequent need for their disposal, and (iii) be designed to minimize the generation of leftovers.

Packaging constitutes waste in its own right, with a set of concerns distinct from APIs; it can also complicate processing of disposed drugs or introduce new demands for disposal (such as when sophisticated delivery devices are used). Packaging adds a number of variables and determinants in the disposal of drugs themselves. Depending on its design, packaging can dictate what route of disposal a consumer might select (e.g., bingo cards are not conducive to flushing), it can increase the quantities of medications that are eventually disposed (e.g., large, bulk-size containers of hundreds of doses that expire before use), or it can reduce the quantities of drugs being disposed (e.g., drug dispensing containers that improve patient compliance). Many other possibilities are also at play.

Drug products could be designed and packaged with the need for their eventual disposal as a primary requirement. And proper design must take into account the fact that the needs imposed for disposal might differ for used medications versus unused medications. Any special considerations that might be necessitated by disposal need to be integral criteria at the start of the drug design cycle.

Innovation in packaging design and function could play a key role in the drug disposal conundrum. By improving compliance, fewer medications would require disposal. And by adding improved safety features, fewer poisonings would result. By implementing a refundable deposit fee on the container (which could be warranted with sophisticated recyclable containers), consumers would also be encouraged to return to the pharmacy, increasing the odds of communication with the pharmacist and further improving compliance.

A possible downside to adoption of new types of packaging is that the array of leftovers could become much more confusing to the eye, possibly further complicating waste collections. Packaging also adds to the burden of solid waste and can increase the difficulty in dealing with drug residuals that remain in devices. Almost nothing is known regarding the fate of packaging materials (or their API residuals) in landfills.

Advancements in package design have not been fostered by academic research - partly because there has been little demand from the pharmaceutical industry. Impetus has come primarily from consumers and the government (e.g., child-resistant closures) and from private sector research and development. Several overviews of packaging design and technology used in the pharmaceutical industry are available (Bauer 2009; Freedonia Group 2008).

Pharmaceutical packaging and delivery devices will pose increasing challenges for medication disposal, especially as the medication and the packaging begin to merge as an integral whole (such as the integration of electronics). One example of an electronic delivery system is the Ionsys system using fentanyl. The Ionsys is an iontophoretic transdermal system that provides on-demand dosing. As demand for innovation in pharmaceutical packaging grows, new challenges will continually arise with respect to disposal.

Few take-back programs currently recycle conventional containers separately. One exception is ElephantPharm (ElephantPharm 2010).

The presence of residual APIs in used delivery devices and certain containers poses a major route by which APIs can enter landfills. Comparatively little consideration has been devoted to the design of packaging that allows complete dispensing of API contents or that facilitates separation of the API from the packaging prior to disposal. A sustainable approach to disposal must consider the disposition of the medication containers, packaging, and devices (Dillon and Rubinstein 2005b).

One example of a delivery device that may contribute unnecessarily to solid waste is the device used with pressurized metered-dose inhalers (MDIs). Each MDI comprises a canister, which contains the formulated API, and a plastic inhaler actuator (or "boot"). Each MDI is dispensed with a new "boot." As an alternative, MDIs dispensed in multiples could be dispensed with only one boot, or consumers could opt to reuse old boots for new prescriptions. Alternatively, MDI boots could be made from biodegradable polymers. Orally inhaled and nasal drug products (OINDP) tend to be at the forefront of design of new delivery devices. They would therefore make likely candidates for factoring in the potential solid waste footprint during design. Another step in reducing the environmental footprint would be the development of self-contained mechanisms for deactivation of the API residuals remaining in used devices - analogous to the approaches that are being explored for transdermal devices (Cubbage et al. 1998; Warner et al. 2005).

An example of what can be accomplished with innovative packaging is the NextBottle (One World DMG 2010) - a sophisticated design that attempts to address all of the major limitations of conventional containers. The NextBottle attempts to provide a container that does not resemble conventional pill bottles and at the same time provides unit dispensing, indication of day of dispensing, better protection from humidity and oxygen, and child resistance while improving ease of opening by adults. The intent is a container that reduces accidental poisonings while improving patient compliance. The ability of the medication manufacturers to customize the graphics on the container could also reduce medication errors, especially for patients with multiple medications on complex dosing schedules (polypharmacy). Some of the recent package redesigns have attempted to address a range of problems at once. One that tries to address child-resistance and a number of aspects dealing with compliance is the Key-Pak (Keystone Folding Box Co. 2010).

Packaging is a major determinant of API stability and therefore real-world expiration. Many approaches are possible for extending the time to where medications require disposal because of expiry. Examples include more effective oxygen and moisture scavengers and better ways for protecting against heat, humidity, and light. One possibility would be the development of "smart" or "intelligent" packaging systems - such as those used in the food industry - where the objective would be lengthening shelf life and/or monitoring and providing real-time indication of the quality of the medication and whether it is approaching expiry (whether the storage conditions have been adequate, such as proper temperature, humidity, light, and duration). Knowing the actual shelf life (which is a complex function of storage conditions and time) could prevent the unnecessary, premature discarding of medications. The issues surrounding package redesign and expiry are discussed by Daughton (2003b).

Instead of adding to the solid waste burden, packaging and devices could be diverted to more useful purposes. "Repurposing" or "up-cycling" reclaims constituent materials for uses that do not match their original purpose. Repurposing has already been implemented in the medical waste arena by Sharps Inc, in their "Waste Conversion Process" that repurposes used sharps, syringes, and certain other medical devices into raw materials used in fabricating other non-medical products; one outcome of this work has been development of a product called PELLA-DRX™ , which can be used in the manufacture of many non-medical products, including cement (Sharps Compliance 2010b).

Of peripheral relevance, the packaging used for physician samples can differ from that of dispensed drugs. The average weight for the packaging used for samples is substantially greater (Pai et al. 2000).

Role pharmaceutical promotions: sampling, detailing, DTC and drug data mining

Manufacturer promotions are a contributory source to the need for drug disposal and for overall pharmaceutical usage, which serves as the main source for API residues in the environment (via excretion). This topic was covered in Ruhoy and Daughton (2008). Some additional perspective will be provided here.

Promotions take place in the healthcare environment (referred to as "detailing" of sales representatives), where free samples are often provided (referred to as "sampling") primarily to physicians and sometimes to pharmacists. It also takes place directly to the consumer in the form of direct-to-consumer (DTC) advertising. New and independent analysis of the investment in promotions made by pharmaceutical manufacturers shows that they exceed investments in R&D (Gagnon and Lexchin 2008). Many types of promotions are employed and are continually evolving. Included are the less-recognized forms such as ghostwriting and illegal off-label promotion; "seeding trials" and educational grants can also sometimes be included. Gagnon and Lexchin (2008) conclude that in 2004, promotions per physician amounted to $61,000. Promotions accounted for one quarter of sales dollars versus only 13% for R&D. So about twice as much was spent on promotions as on R&D. The significance of this with regard to leftover drugs is that a certain (but unknown) amount of promotions may contribute to distribution of free samples and to imprudent or unnecessary prescribing (and eventually dispensing). When the consumer experiences a lack of perceived benefit or side effects, the course of the medication is ceased (non-compliance) (Gagnon and Lexchin 2008). Lo and Field (2009) present discussions regarding conflicts of interest at the interface between the practice of medicine and the pharmaceutical industry.

An overview of how pharmaceutical marketing can affect the practice of prescribing is presented by Rodríguez Mari (2007). Pomerantz (2004) argues that DTC advertising and other drug company marketing practices to physicians (e.g., provision of free samples that only comprise expensive, brand-name medications) attempt to shift consumers to higher-cost but not necessarily better drugs. This serves to inflate patients' expectations, eventually leading to unmet expectations, followed by early cessation of the remaining course of medicine (non-adherence). Pharmaceutical Research and Manufacturers of America (PhRMA) maintains that DTC can

improve patient compliance (PhRMA 2008b); no peer-reviewed studies, however, were located in the published literature to support this stance, nor were any studies cited in the PhRMA report.

It seems that the limited evidence points to promotions such as DTC as possibly being interconnected with the issue of patient non-compliance and therefore a factor leading to leftover drugs. Promotions such as sampling have more direct connections with drug wastage, as a result of expiration. Locating, deciphering, reading, and tracking expiration dates on physician samples can be surprisingly difficult and time consuming. This routinely results in accumulation of expired samples in physician offices. Lohiya (2006) has proposed a labeling system to assist physicians.

In attempts to avoid the problem with expiration, donation of unwanted samples by physicians is often pointed to as a solution. But the practice of physicians donating unused drug samples to "free" (charitable) clinics is controversial, as provisions of the US FDA Prescription Drug Marketing Act (PDMA) prohibit distribution of drug samples "except by the manufacturer or an authorized distributor of record"; see page 776 under the heading "Responsible Reuse, Recycling, and Donation" in Daughton (2003a). A discussion of the law with respect to donation of free samples can be found in McKee (2006, see page 53).

One argument in favor of sampling is that free samples serve as a "safety net" for those in need and cannot afford medications. The counter argument is that they simply serve as a marketing tool directed only at those who might later commit to purchasing. A finding from Cutrona et al. (2008a) is that free samples are primarily given to those who can afford to buy longer-term prescriptions. A letter in reply to Cutrona (2008b) maintains that providing free samples to the poor represents a disservice because they would not have further access to expensive brand name medications once the samples expire. This could also cause medical problems when a course of treatment is terminated early. A number of reasons are provided for not providing free samples to the indigent (Cutrona et al. 2008a; b; Vincent et al. 2008).

The study by Cutrona et al. (2008a), however, was deemed flawed in several press releases by PhRMA (PhMRA 2008; PhRMA 2007; 2008c). Although PhRMA's main argument is that sampling is needed as a source of free drugs for the indigent, the creation of the Partnership for Prescription Assistance (PPA) would seem to have largely accomplished that purpose (PPA 2010).

In PhRMA's "Code on Interactions with Healthcare Professionals" (PhRMA 2008a), their stance on sampling is clearly stated: "It is appropriate to provide product samples for patient use in accordance with the Prescription Drug Marketing Act." PhRMA implemented a voluntary ban on gifts in 2008.

Only in the last several years have some manufacturers begun to become sensitive to the issue of promotions (Weintraub 2008). A comprehensive overview of the many issues surrounding sampling is available from Chimonas and Kassirer (2009). The use of free samples possibly subordinates a more prudent, cost-effective evidence-based approach to prescribing, as it encourages the use of more expensive newer drugs. On the basis of existing evidence, Lo and Field (2009) recommend that clinicians should not accept free samples.

An organization that has actively argued against the practice of sampling and other drug company giveaways in the physician office is "No Free Lunch" (Goodman 2010). Only recently has the concept of educating physicians about the negative aspects of promotions emerged. "Counter-detailing" is used by organizations that visit physicians to provide evidence-based advice on prescribing and attempt to discourage the ad-hoc, blind acceptance of free samples. One example is the SCORxE program (SCORxE 2008).

Sampling also has links to drug diversion, which is known to be practiced by both sales representatives and doctors (Chimonas and Kassirer 2009).

Regardless of the usefulness of sampling, most of its negative attributes could be reduced if physicians employed vouchers, where patients could then obtain the free samples from the pharmacy. This would greatly reduce the problems with expiration, diversion, and leftovers (as a portion of patients are known to accept free samples with no intention of ever using them, and might then choose to not have the voucher filled).

Finally, there is one aspect of the many inter-connections between pharmaceutical manufacturers and prescribers that is indirectly tied to promotions. It purportedly can have major ramifications for whether a particular drug will be successful and experience an increasing sales trajectory. Physician prescribing data has long been available to pharmaceutical manufacturers. These data are called prescriber-identifiable [PI] data. PI data are mined by health information organizations (HIOs) such as IMS Health. These data are specific to individual physicians. PI data are used for a wide array of purposes, including monetary compensation for sales forces (Steinbrook 2006). One of the outcomes of this practice is that PI data ultimately can be used to influence physician prescribing practices and behavior. One example is the concern that use of PI data could shift a physician's prescribing behavior away from a generic drug and toward a branded drug. PI data can also be used to increase drug usage. Bans on PI data mining have already been enacted in three states: New Hampshire, Vermont, and Maine. Over a half dozen other states have introduced legislation to restrict mining of PI data (Chernove et al. 2009).

Roles of counterfeiting, importation, and Internet pharmacies

Counterfeiting is partly inter-related to diversion, as not all counterfeiting results in fake drugs (those containing no API) or in drugs containing APIs different from those that should be present (undeclared APIs). A portion of counterfeiting relies on the use of legal drugs (obtained by theft) already in legitimate distribution channels. This could simply involve the repackaging of legitimate drugs; for example, expired or nearly expired drugs can be relabeled with new expiration dates and reintroduced to the legal distribution system (Hileman 2003).

Counterfeiting can contribute in two primary ways to amplifying the quantities of APIs entering the environment: first by introducing more APIs (both legal and illegal) that would not otherwise be dispensed as a result of legitimate prescribing, and second by diverting legitimate drugs from the normal distribution channel and thereby requiring the manufacturing of additional inventory to make up the difference (to meet legitimate prescribing/dispensing needs); clandestine manufacturing also introduces APIs and other wastes associated with synthesis and formulation

to sewers and waterways. When a drug shipment is stolen (and even if subsequently recovered), often the manufacturer is required to recall and destroy all existing supplies - further compounding the problem (Duggan 2010).

Counterfeiting can involve whole, formulated drugs diverted from the legitimate system of distribution and then introduced back into the system; this is often accomplished via the gray market (an ill-defined market that serves as the interface between the legitimate and illegal markets) - or sold directly within the gray market itself. Or it can involve the clandestine synthesis of APIs (some of which might be bona fide), which are then used to illegally manufacture drugs anew. These clandestine drugs may or may not contain the API(s) declared on their labels, and they may also contain a bewildering array of adulterants (including undeclared APIs) or other contaminants as a result of not following good manufacturing practices (Daughton 2011). These counterfeited drugs are then introduced into the legitimate distribution system or sold on the gray market. The interface between the legitimate and illegal drug markets can be very nebulous and hard to define (Daughton 2011).

Overviews on counterfeiting are presented by Hileman (2003) and Jackson (2009). Counterfeit drugs are also used as a way to finance terrorism (Jackson 2009).

The importation of drugs outside the regulatory system of the US is a source of additional drugs with unknown, but likely very large, magnitude. Estimates from the FDA have ranged from millions to tens of millions of packages of illegally dispensed prescription and counterfeit drugs per year. All of these serve as additional contributory sources for leftover drugs by consumers as well as a large source of drugs requiring disposal after confiscation by law enforcement and customs. Importation is a complex issue. A comprehensive overview is provided by the USGAO (USGAO 2005) and Hubbard (2001).

As with drug screening, technology to deter or simply detect counterfeiting is in a perpetual state of evolution. Numerous of technologies, including RFID and holograms, have been tested over the years to combat counterfeiting. Historically, however, each new deterrence technology is quickly subverted or counterfeited itself. An example of current deterrence technology is NanoGuardian, which uses a proprietary nanotechnology-based approach to deterring counterfeiting and diversion (Marks 2010; NanoInk 2010). NanoGuardian imprints each pill with a microscopic logo and a 350-digit random code that is changed daily; this technology has been approved by the FDA and is in the process of being implemented. A much simpler approach that has been tested in Africa, where counterfeiting is rampant (especially for essential drugs such as antimalarials), is the use of scratch-off ID codes on packaging that can be relayed by text-messaging to authenticate the contents (Bennett 13 May 2010); several companies have been involved with this approach, including mPedigree (http://mpedigree.net/), Sproxil (http://sproxil.com/), and PharmaSecure (http://www.pharmasecure.com/products-and-services/product-security/).

A variety of largely illegal means of dispensing drugs serves to exacerbate the entry of APIs to the environment, as a portion of the dispensed medications are received by those who should not be using these medications. Included are Internet ("rogue" or "online") pharmacies, "pain clinics", "pill mills", and others who dispense "under-the-counter." A major focus for these

dispensers is certain controlled substances, especially opiates used for pain treatment. The first Internet pharmacies came online in 1999. Surveys show that while low percentages of drug abusers obtain controlled substances via the Internet, it is suspected that drug dealers may be obtaining their supplies from these rogue pharmacies. Internet pharmacies also play a role in the distribution of illegal drugs (drugs not registered with the FDA, such as designer drugs) (Daughton 2011), as well as diverted and counterfeit drugs (see FDA's page on purchasing drugs over the Internet: USFDA 2010b).

Overviews of the issues surrounding Internet pharmacies can be obtained from: (Barthwell et al. 2009b; CASA 2006; 2007; 2008; deKieffer 2006?; Fox 2004; Lessenger and Feinberg 2008; USGAO 2005). The sale of prescription drugs via Internet pharmacies or Internet auction sites is regulated in the US under 15 U.S.C. § 45(a) by the Federal Trade Commission (FTC).

In response to the advent of Internet pharmacies, the National Association of Boards of Pharmacy (NABP) developed the Verified Internet Pharmacy Practice Sites (VIPPS) program in the spring of 1999 (NABP 2010a); the NABP also operates an analogous verification program for online pharmacies that dispense for companion and non-food producing animals (NABP 2010b). Additional verification programs have followed VIPPS, such as: LegitScript (LegitScript 2010) and PharmacyChecker.com Verification Program (PharmacyChecker.com 2010).

The Ryan Haight Online Pharmacy Consumer Protection Act of 2008 amended the CSA and the Controlled Substances Import and Export Act to prevent illegal dispensing of controlled substances over the Internet. This was accomplished in part by requiring face-to-face patient-physician meetings prior to prescribing (DEA 2009b). Prior to the Ryan Haight Act, National Center on Addiction and Substance Abuse (CASA) had identified 159 web sites offering controlled substances - 85% not requiring a prescription. Only two sites were VIPPS certified.

Role of donations - and recycling, reusing, reissuing

Discussions involving the donation of drugs invariably become intertwined with the topic of drug "recycling"; see page 776 under the heading "Responsible Reuse, Recycling, and Donation" in Daughton (2003a). In turn, the issues surrounding donations and recycling intersect with those of drug diversion and sharing. So discussions on these topics can become convoluted and confused.

Consumers are often attracted to the prospects of donating drugs they no longer want, with the hope that others may benefit. But with few exceptions, consumer donation of drugs is either illegal or misguided.

Drug recycling and reusing are loosely used terms. Neither really conveys the proper intent. While reuse is probably a better term with respect to collecting unused, pristine medications for their subsequent use by new patients, a better term would be "reissuing." Medications are not actually reused, nor are they recycled, as this implies reuse of previously used medications. Drug reissuing must take place within the closed loop of distribution/prescribing. These are conditions that rarely exist - primarily currently limited within long-term care facilities - where the medications never leave control of those providing the care.

Medication recycling is fraught with dangers (such as tampering and self-medication errors). For this reason, it is usually only practiced where tight controls exist on the history of the medication. More information is in Daughton (2003a). The major question is whether safe programs could be developed for drug reuse or reintroduction into the distribution/retail chain.

The history behind state legislation enabling donations and reuse within the US is summarized by the National Conference of State Legislatures (NCSL 2010b). The National Association of Boards of Pharmacy (NABP) is playing a major role in development of policies regarding reuse of medication (NABP 2009a). Their initial efforts have been focused on those medications that never leave the closed distribution loop, such as those dispensed in nursing facilities. The National Association of Pharmacy Regulatory Authorities (NAPRA) in Canada has developed guidance for pharmacists in Ontario for the reuse of medications (NAPRA 2009).

An overview of drug recycling is available from Pomerantz (2004), Struglinski (2009), and (Baaklini 2009, in French). Examples of successful reuse programs for unused drugs exist in the US and Switzerland (Besson et al. 2008; Dispensary of Hope 2009). Despite the laws limiting the practice of recycling in the US, recycling may be even further restricted in other countries, such as Canada (Doyle 2010).

The practice of donation is generally reserved for humanitarian disasters, but is sometimes called the "second disaster" because it generally causes far more problems than it solves, especially when it involves "dumping" (the shipment of expired or near-expiration medications to remedy a pending or anticipated disposal problem or to gain tax advantages). Historically, donation of drugs has essentially been used as a form of geographic "redistribution" - where drugs that are no longer wanted are shipped to other countries. Donations often simply serve to transfer a pending disposal liability from one geographic locale to another - frequently an impoverished country lacking the means or money to properly dispose of medication wastes. Donation of drugs within the US (for example to free clinics), is generally a practice that is prohibited. A summary of the problems surrounding donations is provided by Pinheiro (2008). A focus on the role of expiry is provided by Reich et al. (1999).

The donation of drugs to humanitarian relief operations and charities is an extremely controversial issue - primarily because of numerous concerns regarding human safety (e.g., tampering, terrorist sabotage), disposal, and drug diversion (illegal reselling). While pharmaceutical manufacturers and distributors can participate in donations, no formal guidance exists for the public. The donation of pharmaceuticals unsuited for particular relief efforts has resulted in the need for expensive warehousing of extremely large quantities of drugs that must then be disposed; the added burden imposed by the need for more oversight also diverts personnel from more urgent tasks. The two major reasons that donated drugs can be unusable are that they have expired or do not match the most pressing therapeutic or healthcare needs; other, unanticipated reasons can include illegible labels, labels that cannot be translated, and unfamiliar dosage forms or strengths. This was a large-scale problem for the relief efforts during the Bosnian conflict and later (well after the WHO guidelines were established), such as following the Indonesian Tsunami. Most relief organizations prefer to receive money rather than pharmaceuticals. Drug expiry and appropriateness are two major issues that make donation

programs problematic. With this said, the donation of pharmaceuticals to those charitable organizations that accept certain select drugs (in their original, sealed manufacturer containers) for distribution overseas is a limited option.

Donations for humanitarian emergencies are renowned for creating massive problems with respect to disposal of gross quantities of unneeded or expired medications. This has been repeatedly documented by the WHO and others. Indeed, it was this very problem (the problems imposed by the need to dispose of huge quantities of unwanted medications following the Bosnian war) that prompted the WHO to establish its international guidelines for donations. Despite the fact that these guidelines were published in 1999, they continue to be frequently ignored in relief efforts (Grayling 1999; WHO 1999 [revised]).

Donated drugs are also known to cause human poisonings as a result of poorly labeled or undocumented medications. One such instance occurred in Lithuania, where a veterinary drug (the anthelminthic closantel) with no human use was administered to 11 women for gynecological problems, resulting in temporary blindness and other problems ('t Hoen et al. 1993).

Some of the statistics on the quantities of drugs donated during humanitarian crises are presented by Autier et al. (2002), who also proposed recommendations for improving the handling of donations in future crises. As a result of the conflict in Croatia, thousands of tons of pharmaceutical wastes resulted from foreign donations and required storage in 250 warehouses (Autier et al. 2002). More than a decade after the war (in 2007), hospitals in Croatia still had large repositories of donated drugs stored as hazardous waste (Marinkovic et al. 2008).

As a result of the 26 December 2004 tsunami that struck Aceh, Indonesia, 4,000 tonnes of unrequested medications were received. Despite the issuance of the international guidelines on drug donations 10 years prior by the WHO, the situation had actually grown worse. As a consequence, the Pharmaciens sans Frontières (PSF) [Pharmacists Without Borders] recommended that the WHO guidelines be integrated into national drug policies worldwide and that drug donations be regulated as a public health issue; it deserves noting that donations can also be an environmental issue (PSF 2005).

The quantities of unwanted donated drugs are often so large that they far exceed any capability or capacity to properly dispose of them - whether by incineration or burial as hazardous waste. As a result, much is haphazardly discarded or stored indefinitely (where it poses diversion risks). Many of the problems faced by donation "repositories" are summarized by Wapner (2009). Examples of economic consequences of drug donations are recounted by Ette (2004) and Guilloux (2001).

Drug diversion and sharing (possibly made worse by current disposal guidance)

Informal surveys of those who have dropped off drugs at US take-back events reveal that the vast majority would otherwise have elected to keep storing their unwanted medications at their homes rather than discarding them to trash or sewers. While this may not reflect the behavior of the

general population, the current absence of any prudent way to dispose of drugs other than through a patchwork of take-back events and programs clearly exacerbates the potential for diversion and unintended poisonings in the home setting. One indicator of the diversion of medications from homes and elsewhere is the anecdotal reporting of large quantities of expired medications sold at flea markets.

In reality, medications are located at seemingly countless locations throughout society (Ruhoy and Daughton 2008). Diversion probably occurs from all of these locations. Perhaps the most infamous instance of diversion was discovered in the Shipman Inquiry, begun in 2001. Harold Shipman, a UK physician used controlled drugs diverted from deceased patients to murder hundreds of patients under his care (Royal Pharmaceutical Society 2006).

Drug diversion was a recognized problem as early as the 1950s. A number of overviews of the drug diversion problem are available (CASA 2005; Inciardi et al. 2009; Inciardi et al. 2007). Efforts began in 1959 to amend the Federal Food, Drug, and Cosmetic Act to control diversion from distribution channels. By the early 1970s, the linkage of diversion with abuse and crime had become firmly established (Wochok 1973). Stockdale (2008) compiled over a hundred abstracts of papers dealing with drug diversion, but the full literature is much more expansive. Diversion includes the nonmedical use (NMU) of drugs, which could be as high as 20% (Stockdale 2008). Efforts to control diversion have long been complicated by two opposing needs that require careful balancing: the need to minimize diversion to the black market while simultaneously not restricting access for medical treatment, especially pain treatment. Simply put, the major dilemma for the drug distribution system (especially for the physicians) in the treatment of pain is in balancing the restriction of medications prone to diversion and abuse against the risk of under-treating pain (which requires ready access to medications with high abuse potential). Doctors are caught in between the obligation to treat legitimate pain and the need to be alert to abusive use. The dilemma in finding the right balance in the clinical use of analgesics has been a top concern of the FDA's (Barthwell et al. 2009a; b; Woodcock 2009).

Diversion can occur in numerous ways and places within the drug lifecycle. It ranges from outright theft to seemingly innocuous "drug sharing." Showing why the DEA prefers the closed distribution loop with a system of internal and external controls, diversion occurs even within reverse distributors and sometimes even by their owners (Walsh 2009). Thefts are not uncommon (Solomon 2010) and have even been reported from USPS. Theft of drugs sent through the mail (either new prescriptions or unused drugs being returned for disposal) could eventually become a growing mechanism for diversion. It is most likely also a problem that is under-reported by USPS to the news (Warren 2010). Diversion via theft and burglaries is believed to be underestimated (Inciardi et al. 2007).

At least one report of a new drug diversion scheme has emerged that capitalized on the mere existence of drug collection programs - diversion of drugs from sham medicine collections, made to appear real (Ranger 2010). In a similar manner, diversion could easily occur from sham charity programs set up to purportedly collect medications donated for emergencies. Diversion is clearly a possibility for legitimate take-back programs, and is the major reason the DEA requires the presence of law enforcement when controlled substances are involved.

Leftover drugs represent opportunities not just for diversion and abuse but also for "inappropriate" use, such as self-administration for incorrectly assessed but still legitimate medical needs. A special aspect of diversion is drug "sharing" (sometimes called recycling or reuse). Drug sharing is a more recent twist on NMU, a practice that involves drug loaning or borrowing. An overview is provided by Goldsworthy (2008). Sharing promotes self-medication involving inappropriate or imprudent use, and as such has great risks. Exposure to teratogenic pharmaceuticals (such as isotretinoin), for example, would be a unique concern for drug sharing - particularly for young women. Self-medication can be particularly problematic with antibiotics because of the unnecessary selection for pathogen resistance. Antibiotics are commonly found stockpiled in homes throughout the world for future use (Stratchounski et al. 2003). Any drug with a REMS (Risk Evaluation and Mitigation Strategy) in place could pose critical risks in sharing.

Any measures designed to reduce the incidence of drug leftovers could greatly help in also reducing drug sharing. But it is critical that these measures be designed to not restrict the practice of medical care.

Roughly a quarter of those surveyed reported sharing of medications; rates varied depending on the therapeutic class of drug (Goldsworthy et al. 2008). Estimates in Gulf countries are that 20 to 30% of household members use shared medications (Abou-Auda 2003).

Generally, the reuse or recycling of medications is illegal, especially for controlled substances. The informal sharing of drugs among individuals on small-scale local levels is an increasingly prevalent practice.

Ironically, a major driver of the consumer's desire to "recycle" their leftover medications by inappropriately donating to charities or sharing with friends is the desire to avoid further wastage. The perception is that leftovers (even when expired or hazardous) not only have economic value but also continued therapeutic value. Consumers are frequently highly frustrated that leftovers cannot be put to good use by friends or others in need. The realization that unopened medications cannot be reused and must be disposed can discourage the return of leftovers to collection programs once it is clear that returned drugs are simply disposed. At the same time, one of the reasons cited by pharmacies in avoiding participation in drug returns programs is the potential for the public to suspect that the returned medications would be used to fill new prescriptions (Musson et al. 2007).

While drug sharing is indeed one practice with the potential to reduce the need for drug disposal, it also heightens the potential for poisonings as a result of adverse drug events (ADEs). It can also possibly increase the excretion of API residues above levels that might have normally occurred if the recipients of the shared drugs would have otherwise never been prescribed the medication.

In recent years, exceptions have been granted in certain situations for recycling where the prescription-consumption cycle is closed and highly controllable. This ensures no opportunity for tampering. For example, the recycling of drugs by nursing care homes, such as permitted by Oklahoma's "Utilization of Unused Prescription Drugs Act" (Broyles et al. 2007) allows for the

reuse (reissuing) of non-controlled substances prescribed in nursing care facilities for indigent care. Wider-scale use of computerized unit-dose dispensing technology will continue to facilitate this practice.

Despite the fact that the risk of tampering (adulteration, sabotage, etc) is a major driver behind restrictions on recycling, no evidence was located in the published literature indicating that any instances or poisoning have been reported. But this cannot account for the possibility that instances may have occurred unnoticed.

Worth noting is a practice that intersects sharing and donations. It involves a few select organizations that organize the collection of specific donations from the public and target special uses. They ensure that the collected medications have valid uses by the recipient. One example is the Starfish Project which collects unused antiretroviral medications to support HIV-positive Nigerians (Normal 2008). Another that recycles AIDS medications is RAMP (RAMP 2008). One organization is helping to coordinate excess supply (at the manufacturer level) with real-time needs (at the free clinic level) (SIRUM 2010).

The most important aspect of diversion with respect to drug disposal is whether the two are actually linked. Data are very rare regarding whether drugs are diverted from active household stocks of medications (those still in use for their intended purpose) or from stocks simply being stored by the consumer and awaiting disposal. This is an important point, as it determines how important diversion might be as a driving force for reducing home stockpiles. One of the only surveys to date determined that one in five residents of Washington/Oregon had experienced instances of diversion from their drug supplies. But of this subpopulation, 80% said that the diversion occurred from an active stock; only 10% said the diversion occurred from expired/unwanted drugs (Whittaker 2010, see slide 17). This type of survey needs to be more broadly implemented if a determination is to be made as to whether more timely disposal of medications actually reduces diversion. The data presented by Whittaker indicate little impact. The real question might be whether the dispensed medications or their quantities are necessary to begin with.

There are also special circumstances that unintentionally lead to diversion. For example, many patients admitted for in-patient psychiatric care leave their medications at home, where they can be diverted by others (Robin and Freeman-Browne 1968). This could be easily prevented by healthcare providers inquiring as to what medications the patient has remaining at home and to ensure they are secured or properly disposed.

Diversion is a practice that continually evolves. There are too many varieties to discuss here. Drugs not yet on the market are even known to be diverted from clinical trials (Daughton 2011). There are two types of diversion not yet mentioned, however, that receive significant attention in the press - doctor shopping and hospital shopping. These tend to be used by drug abusers and addicts. These forms of diversion essentially capitalize on otherwise legal means for obtaining drugs - with no outright theft involved. In doctor shopping, patients visit multiple doctors (often for bona fide conditions, but sometimes with faked symptoms) to obtain multiple prescriptions for the same medication (often opiates); the physicians are not aware of each other's prescribing

for the same patient. Hospital shopping is a variant where free emergency services are duped into prescribing unneeded drugs for faked conditions (Sullivan 2009).

To deter "shopping," prescription drug monitoring programs (PDMPs) have been established in various states (41 states as of early 2010) (NCSL 2010a). PDMPs track pharmacy dispensing of controlled substances. Physicians can request reports that list all medications that a patient has received over a 6-month period. These programs, however, are not standardized and do not communicate well with each other. There also is no requirement to make use of PDMPs, and the system is easily circumvented by motivated drug abusers (Park 2010). The Department of Justice is attempting to improve the PDMP system. It has selected the Heller School for Social Policy and Management (Brandeis University) to work on a new initiative for reducing diversion: the "PMP Center of Excellence" (Brandeis University 2010).

Drug disposal for reducing diversion and abuse

While the threat of diversion and abuse was the original driver behind development of the ONDCP disposal guidance issued in February 2007, and which was revised in 2009 (ONDCP 2009 [updated October]), no study is evident that has tried to distinguish the origin in households of medications being diverted or abused. As with poisonings, it is known that diversion and abuse is a major problem. But it is not known to what extent expired drugs or drugs awaiting disposal are contributors to the problem (as opposed to medications still being actively used for their intended purposes). Clearly, a drug's owner will notice reductions in their supply of actively used medication more readily than reductions in those medications no longer being used and which should have been disposed; so it is possible that diversion from stocks of drugs no longer being used could be important. But also, as with poisonings, used delivery devices such as transdermal patches (especially those containing opioids) are a known source of abuse (e.g., via reapplication to the skin).

Without research specifically targeted at determining the relative proportions of medications diverted from household stocks that are still in active use versus those awaiting disposal (or those just disposed to trash), it can only be assumed that ridding homes of unwanted drugs will help to reduce drug diversion or abuse.

Drug disposal as a contributor to ambient environmental levels

Just as with the incidence of poisonings, the significance of drug disposal to sewers as a contributing source of APIs to the environment is unknown and controversial. In brief, no definitive statements are yet possible. Broad generalizations are not possible because the contributions undoubtedly vary immensely among individual APIs. The contributions from disposal probably vary depending on the individual API, as the rate of non-use can vary dramatically across medications and the degree of excretion varies from nearly nil to nearly 100%. The rate of non-use can also vary among individuals, posing great challenges for modeling. Clearly, disposal of a medication containing an API that can be extensively metabolized (little would normally be excreted unchanged) holds a much greater potential for contributing to its environmental loading than would a medication containing an API that is largely excreted unchanged (Daughton and Ruhoy 2009a). Stated another way, generally an API

that would normally be excreted unchanged (not altered by metabolism) has a greater chance of contributing to its environmental levels when used as intended (e.g., ingested) compared with when it is disposed to sewers.

Disposal's contributions may very well prove significant for a select few medications. But for many or most others, it will undoubtedly prove minuscule. Many figures on the contributions from disposal have been recited in the non-peer-reviewed literature and at conferences but they lack any supporting data. Most are based on conjectures or guesstimates.

The use of collection programs for leftover drugs to reduce the occurrence of APIs in waterways does not yet have a science-based justification. To date, no study has performed an assessment of the effectiveness of take-back programs in reducing API levels in sewage or the environment. The need for data showing the relative contributory role played by disposal in the occurrence of APIs in the environment was identified as a research gap in EPA-ORD publications as early as 2004 (Daughton 2004; 2007). There are few other publications (e.g., Houskeeper 2009) that highlight this unknown, and fewer yet that point out the lack of this evidence for justifying the need for take backs. *This means that much of the ongoing effort in developing drug collection programs based on protection of the environment lacks a body of supporting data for justification*.

Representing the view that disposal to sewers is a comparatively unimportant source is the perspective of PhRMA. Those involved with PhRMA's workgroup on pharmaceuticals in the environment (PiE) (Anon 2010; Finan and Wood 2008; Finan et al. 2007) maintained that the contributions of APIs to sewers via drug disposal are practically insignificant: "Even with current disposal practices, drain disposal of unused medicines is very unlikely to contribute more than 10% of the APIs found in WWTP influents." "It is likely that there would be little effect (less than a 1 part per trillion) on WWTP API influent concentrations as a result of implementing unused medicine take back programs compared to household trash disposal." "Either household trash disposal or take back programs can reduce the unused medicine contribution of APIs in WWTP influent to < 1%".

From a different perspective, perhaps the first (and only) attempt at quantitative modeling based on actual data for APIs disposed to sewers was published in 2007 (Ruhoy and Daughton 2007). Calculations done for the disposal of carbamazepine by a county coroner’s office estimated a concentration in raw sewage influent of 1.4 ppt (1 ng/L). This is significant, as it represented the disposal practices from but one small sector of society. The most in-depth examination of the possible role of disposal in contributing to ambient environmental residues was presented by Daughton and Ruhoy (2009a); among the many findings was that disposal could possibly serve as a major source of certain select APIs in the environment – primarily those that are extensively metabolized (poorly excreted).

In contrast to landfills that do not receive biosolids, APIs in the aquatic environment have origins from excretion (including bathing, which releases residues not just from topical drugs but also APIs excreted through the skin via sweat) as well as from direct disposal to sewers. As for disposal, its overall contributory role played versus excretion is completely unknown. Stated another way, if disposal of unwanted drugs to sewers were to immediately cease, it is unknown

what effect this might have on residue levels in the aquatic environment. It is probable, however, that if changes in aquatic levels could be detected from cessation of disposal, they would likely be a function of the individual type of medication - perhaps significant for some medications but not for most.

To show the difficulty is establishing the contributory role of disposal to APIs in the aquatic environment, three approaches can be considered, but are primarily useful solely for hypothetical purposes (Daughton and Ruhoy 2009a). One of these approaches relies on the acquisition of comprehensive data on the types and quantities of medications that might be disposed to sewers during a defined time interval. These data would be used to calculate estimated virtual concentrations that would result in the sewage over this time. This requires that the population surveyed for disposal is the same as the population served by the sewage treatment plants (STP). These concentrations would in turn need to be compared with actual, measured API concentrations in the raw sewage from the same STP used to service the population from which the disposal data were acquired. Even then, conclusions would be difficult to draw because the virtual and actual concentrations are acquired during different periods of time and because a major assumption is that the virtual disposal to sewers is occurring evenly over time (no transient change in levels). Moreover, API levels may vary widely not because of actual changes in levels, but rather because of bias and error inherent in the way sampling is performed (Ort et al. 2010b). Such a study would entail great effort.

The second approach would try to rule in or out whether disposal of a particular API simply has the potential to add significantly to environmental burdens. This relies on a thorough understanding of the human pharmacokinetics of each API. For those APIs that are normally extensively metabolized (with little parent API being excreted unchanged or as a metabolic conjugate), disposal could play a significant role (since excretion would be contributing very small amounts) (Daughton and Ruhoy 2009a). For those APIs that are extensively excreted unchanged, the probability is considerably lower that disposal would play a significant role. Other factors, however, can greatly complicate these assessments - for example, the compliance/adherence rate of a drug. For those drugs with very low compliance, a greater portion will go unused, increasing the portion that might be disposed.

The third approach assesses the route of dosing. An example is those medications containing APIs in transdermal devices and which are also not generally used in oral or topical dosage forms. The disposal of these used (or new) devices to sewers could serve as the major or only source of API residues in the environment; examples include transdermal rotigotine, flurandrenolide, and lidocaine.

So we see that pharmacokinetics, exclusive dosage forms, and incidence of patient compliance/adherence are three critical variables that must be known to assess the magnitude of any contributory role for APIs in the aquatic environment played by drug disposal to sewers. To model whether a particular API in the aquatic environment originated from disposal or from other sources (such as excretion) is an extremely complex undertaking. Sufficient data are simply not available for the many variables involved in the factors of such a model. For those APIs that are extensively excreted unchanged (i.e., they undergo little metabolic alteration or tend to be excreted as reversible conjugates) or for those formulated into medications that have unusually

high rates of patient compliance (which results in proportionately few leftovers), disposal to sewers would probably only add immeasurably to environmental residues.

With this said, some generalizations can be made:
(1) Disposal of APIs that would otherwise be extensively metabolized will tend to be responsible for larger percentages of the respective APIs in the environment.
(2) Disposal of APIs that would otherwise be extensively excreted unchanged will tend to be responsible for smaller percentages of the respective APIs in the environment.
(3) For APIs that tend to be used primarily in topical applications, the significance of disposal is a direct function of the portion disposed versus the portion used as intended but not absorbed (as well as the degree to which the medication is incompletely used).

The two extreme scenarios that maximize and minimize the significance of disposal are, respectively: (1) disposal of a large fraction of an API that would otherwise be extensively metabolized, and (2) disposal of a small fraction of a drug that would otherwise be excreted largely unchanged (or of topical drugs). The former is amplified when the API is purchased in large quantities, and the latter is made even less important when the API is purchased in small quantities.

Drug disposal as a contributor to higher episodic spikes of APIs to the environment

One aspect of drug disposal that distinguishes itself from the combined contributions resulting from excretion is its ability to contribute episodic spikes in concentrations when a large quantity of a medication is disposed to a sewer. Regardless of what percentage of APIs in the environmental might be contributed by disposal, the very nature of disposal could lead to transient, episodic spikes in the concentration of whatever API is being disposed via sewage. These concentrations might be orders of magnitude greater than what are being continually introduced via excretion. The significance of these hypothesized intermittent or episodic transient surges in concentrations is not known. Normally, excretion and bathing (two routes that probably lead to constant low-level input to sewerage) establish a continual presence in the aquatic environment for many APIs (imparting "pseudo-persistence" for those whose short half-lives would ordinarily lead to rapid losses) (Daughton 2002). Unknown is whether intermittent discharge to sewers of large quantities of particular drugs could possibly generate spikes leading to concentrations sufficiently high to have adverse effects on microbiota in sewage treatment facilities (STPs). Although transient spikes in API concentrations at STPs have never been demonstrated in real-world conditions to result from disposal, they could perhaps explain some of the excursions in concentration values often seen during environmental monitoring; this is an often observed problem for discrete sampling (e.g., grab samples) versus time-weighted integrative sampling (Ort et al. 2010a). The ability to apportion environmental loadings of APIs to specific sources would clearly be very useful in designing source control strategies. But very few apportionment studies have even been performed. One recent study, as an example, limited its investigation to hospitals (Ort et al. 2010a).

Proper disposal is not the only approach for reducing ambient environmental levels of APIs

Despite the lack of evidence for whether drug disposal to sewers is a meaningful contributor of APIs in the aquatic environment, it has attracted the primary focus with regard to crafting guidance, policy, and regulation - at local, state, and national levels worldwide. This has certainly created a contradiction with respect to assessing risk and benefit, especially given the significant costs associated with the collection of leftover drugs by take-backs. The rationale usually provided for this inconsistency is that disposal is the one aspect of API pollution that is under the control of the consumer and that other end-of-pipe solutions, such as wastewater treatment, are costly and not completely effective. This rationale was used, for example, by the National Association of Clean Water Agencies in a letter to the DEA (NACWA 2009b): "Arguments have been made that the quantity of pharmaceuticals that would be kept out of the sewer system and the Nation's waters through a nationally coordinated take-back program is small, but currently this is the only controllable source of pharmaceuticals entering the environment."

Such statements, however, misrepresent the range of options actually available. This stance could also serve to distract from the real issue and therefore delay progress toward a more sustainable solution. The belief that only the fate of leftover drugs (via disposal) is under the consumer's control is simply not true. Numerous actions can be taken to reduce the incidence of leftover drugs. Many of these actions would also have collateral benefits for human health and safety as well as for healthcare. This is the focus of the concepts of the Green Pharmacy and pharmEcovigilance, which strive to redesign all of the systems involved with medication with sustainability as the major objective. This is where a concerted focus could have enormous impact. Indeed, this is partly recognized by NACWA (2009b) and others, but usually only in passing: "Minimizing the amount of unnecessary medications will greatly reduce the costs associated with their disposal and destruction."

With these points aside, a major point is missed in all discussions surrounding drug disposal. Green pharmacy and stewardship actions designed to improve the effectiveness and efficiency of drug usage will have collateral benefits that extend beyond improved therapeutic outcomes and reduced medication cost. **Any action that results in reduced usage or personalized adjustment in lower dosages will necessarily also result in reduced excretion of API residues. Excretion of unmetabolized APIs (and biologically active metabolites) is a constant factor that has been touted as uncontrollable. The many actions discussed in the body of ORD work cited in this report, however, point to the fact that excretion is indeed a variable that is under the direct control of consumers and the healthcare community and it can be reduced by any number of a wide array of approaches.**

Disposal of drugs to landfills

Drug disposal via household trash may serve as the major source of APIs in landfills not receiving biosolids. The highest levels of APIs in the environment (in the US) have been documented in landfills and biosolids, where levels can reach into the parts per million - levels

that are 3 or more orders of magnitude higher than in the aquatic environment. Occurrence of APIs in landfills not receiving biosolids most likely originate almost exclusively from disposal of whole and crushed, unwanted medications (both solid and liquid dose forms); secondary sources can be hypothesized, such as API residues excreted into diapers or residues on discarded items such as unlaundered fabrics that have absorbed sweat or contacted other body fluids, or items used to wipe dermally applied drugs from the skin (Daughton and Ruhoy 2009a). Medications in landfills then have the potential for wildlife exposures (such as for scavengers) or diversion by those who glean from trash. APIs in landfills with liner defects also have the potential for entry into groundwater via leachates.

In the absence of alternative means of collection, disposal to landfills may be one of the best current approaches to containment of APIs; alternatives are incineration or combustion in waste-to-energy facilities. A primary concern with landfill disposal, however, is the potential for "gleaning" by humans and the possible ingestion of medications by scavengers (raccoons, coyotes, raptors, pigs, and bears, being examples; rats and mice could be particularly problematic should they get poisoned and their carcasses then serving as food for raptors and snakes). The major problem is that there is scant published literature to support either side of the argument.

The occurrence of APIs in landfills would be expected to increase as a result of current disposal guidance. Paradoxically, little is known regarding the extent, frequency, or magnitude of API disposal to landfills or the fate of APIs in landfills. Perhaps the first comprehensive investigation of drug wastes in landfills (and the first and only hand-sorting inventory of municipal solid waste for drugs) was conducted by Musson (2006).

The rate at which drugs are discarded into the trash varies wildly. Musson and Townsend (2009) cite data ranging from 3-65%. On the basis of an assumed 60% discard rate, the calculated estimated API content of municipal solid waste in the US was 45 mg/kg. Actual sampling of waste yielded a content of 8.1 mg/kg, comprising 22 distinct APIs. This represents the only quantitative inventory to date of APIs in municipal solid waste.

If the ONDCP disposal guidance were fully complied with, the API content of municipal solid waste could perhaps be expected to rise sharply (from redirection of drugs disposed to sewers) - as the content measured by Musson and Townsend (2009) was obtained the year before (in 2006) the ONDCP guidance was issued.

Only about three dozen studies involve certain aspects of APIs in landfills or landfill leachates, with fewer than a dozen providing substantive data (Barnes et al. 2004; Behr et al. 2009; Buszka et al. 2009; Geurts et al. 2007; Metzger 2004; Musson 2006; Musson and Townsend 2009; Tischler et al. 2008). The first extensive characterization of landfill leachate for a wide range of APIs was reported by Behr (2009). The data from this study also included ingredients from controlled substances and illicit drugs; some of the reported concentrations were quite high. The first reports of APIs in ground waters influenced by landfills appeared in the early 1990s (Eckel et al. 1993; Holm et al. 1995).

With an increased emphasis in the US on disposal of leftover drugs to trash, the opportunities and likelihood for diversion by, or unintended exposure to, waste handlers and landfill personnel

could be heightened. Indeed, in a survey done in Turkey, over 90% of consumers dispose of drugs in household trash. This posed concerns regarding not just the potential for environmental impact, but particularly with regard to the potential for reuse or diversion by those who glean trash at landfills (Uysal and Tinmaz 2004).

An often reported anecdote involves the disposal of drugs into sharps containers by healthcare personnel. Operating under the assumption that these drugs could then be inadvertently incinerated, some states instead divert sharps to landfills. This represents an unintended disposal of drugs to landfills. Product recalls could result in unusually high transient loadings of disposed APIs. The massive recall of children/infant OTC medications beginning in April 2010 may have prompted the discarding of unusually large quantities of medications in trash (as advised by the manufacturer) as well as the sewer (as many still practice); see links at:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm210442.htm
http://www.mcneilproductrecall.com/page.jhtml?id=/include/new_recall.inc

Given the concerns regarding containment, certain practices in limited use for drug disposal may serve to significantly delay the possibility of leaching. The UK, for example, pioneered development of various "kits" and patents that claim to encapsulate medications - immobilizing them within some sort of polymer. One is the DOOP kit. In the US, several kits have been recently developed (F.P.R. Inc. 2010; Parrott 2010; Rx Disposal Solutions 2010). None of these, however, has ever been evaluated for long-term effectiveness in providing a sustainable solution. Encapsulation could, however, mollify any potential problems with gleaning and animal scavengers at landfills.

Also regarding encapsulation is the use of cementation (inertization), practiced to a very limited degree in the US (e.g., Albuquerque, NM); this is apparently a result, however, of a New Mexico state law that allows incineration only for drugs admitted into evidence for legal proceedings. No research has been published on the fate of APIs from concrete weathering in landfills, but cementation has been widely used in the management of hazardous and radioactive waste. Note, however, that the weight of concrete (ca 1,000 lbs per 55-gal drum) would be a significant factor in energy/transport cost for lifecycle analysis.

Countries having formal drug-returns programs generally prohibit the discarding of prescribed human drugs in trash or the sewer. Perhaps the first metropolitan area in North America to specifically ban the disposal of drugs in household trash is Metro Vancouver (BC) (Metro Vancouver 2010). The stance by Metro Vancouver and that of PhRMA, which maintains that landfilling is the preferred alternative in the US (Finan and Wood 2008), clearly represent contrasting views.

One of the first proposed bills in the US (S7998), which would require manufacturer collection of unwanted medications (Maisel and Englebright 2010), would also prohibit "the disposal of any drug by hospitals and residential health care facilities as mixed solid waste in a landfill."

Incineration

Incineration has been long practiced for medical waste, but its primary objective has been to treat infectious waste. Most of the published literature on medical waste management via incineration focuses on biological waste, sharps, and plastic refuse. Drugs have been viewed essentially as hazardous waste. Historically, as with municipal solid waste, the concern regarding incineration of drugs (and plastic containers) has focused on the generation of priority pollutants (such as dioxins, NOx, SOx, ammonia, and metals) rather than the fate of APIs themselves. This is especially true since the relative masses or volumes of APIs would undoubtedly be many orders of magnitude lower than the containers and other packaging waste. The main variable with respect to incineration is the specific facility design and whether the incinerator is operated within its design specifications; even transient excursions outside operational limits (such as temperature) can cause release of unpredictable emissions. Little research has been done on the fate of APIs during incineration. Drawing general conclusions would also be difficult since the reactions during combustion/pyrolysis are highly complex functions of the incineration deign, temperature regime, oxygen supply, and co-reactants. Maintaining a suite of proper conditions within a narrow range is critical. Incinerators of insufficient temperature (or those having excursions beyond design parameters) could theoretically emit API pyrolysis or combustion products - or perhaps even unchanged parent API.

Only a couple dozen articles in the DDS database are relevant to incineration and drug waste. Several of the more recent or significant articles include: Ciplet (2009), Prüss et al. (1999), and Zhao et al. (2009). The related technology of waste-to-energy (WTE) reclaims the energy content of the waste by generating electricity (McKenna 2009).

Two particular forms of incinerators may pose concerns extending past the conventional concerns of regulated pollutants. One is the makeshift incinerators sometimes used in developing nations and during humanitarian relief efforts. Another involves portable units often employed by law enforcement for destroying comparatively small quantities of confiscated drugs. A common design for small mobile incinerators is the cyclonic barrel burner. One example uses a 55-gal drum fueled by wood or charcoal with a blower to deliver air (Elastec/American Marine 2010). Little has been published regarding the performance characteristics of small or portable medical incinerators (Rogers and Brent 2006; Vollmer 27 August 2010). Pulmonary exposure to combustion/pyrolysis products or to the parent API could be a concern.

Since these rudimentary incinerators lack catalytic or scrubbing capabilities, they have the potential to emit not only a wide range of hazardous combustion products and particulates, but also unaltered parent APIs or partial pyrolysis products from APIs. Pulmonary exposure to APIs or combustion/pyrolysis products of unknown composition poses exposure risks since it is such an efficient absorption route. While these devices were originally intended for use by law enforcement, they could find use by emerging community collection events not familiar with environmental regulations.

One possible pathway of disposal rarely mentioned is open-air burning of residential trash, as still practiced in certain rural parts of the U.S. and the world. In rural Lithuania, the most common route of disposal may well be burning in trash, practiced more often than disposal to

sewers (Kruopienė and Dvarionienė 2007). Other isolated reports include "burning in fire" (Forbes et al. 1989).

Sustainability/Stewardship/EPR

Discussion regarding the sustainable use of pharmaceuticals has yet to attract the attention it requires. Sustainable use extends far beyond prudent disposal. Originally formulated as an integral aspect of the Green Pharmacy concept (Daughton 2003b), it has since been a focus of fewer than a couple dozen articles in journals and books - some the result of this project.

Up to now, reducing the entry of drugs into the environment has focused primarily on end-of-pipe solutions – improving wastewater treatment and in reducing the disposal of drugs to drains (e.g., with consumer drug-collection events such as take-backs). Efforts in preventative actions, such as limiting initial prescribed quantities (e.g., Cook 2009), have been extremely limited. In practice, however, there are countless other options for preventing or lessening API entry to the environment; some of these were discussed for the first time in 2003 under the concept of the "green pharmacy" (Daughton 2003a; b) and under the new concept of pharmEcovigilance (Daughton and Ruhoy 2008b; 2010). These fall under the rubric of environmental stewardship. These options could prove much more effective and more sustainable - reducing the environmental footprint of health care and pharmaceuticals while at the same time improving the quality and efficiency of healthcare. The major impediment for implementing these other approaches is the need to engage and coordinate the active participation of a wide array of stakeholders, beneficiaries, and agencies, especially the various healthcare communities, pharmaceutical and pharmacy industries, and the health insurance industry.

All aspects of the drug life cycle are potential targets for a holistic stewardship program. Many involve alterations to prescribing and dispensing practices. These include: drug substitution, drug quantity (amounts suitable for one course of treatment), drug formulation (easier or more effective delivery systems), lower doses (e.g., achieved with alternative delivery routes or personalized doses), dose timing (e.g., chronobiology), pharmEcokinetic factors (e.g., drug half-life in environment; excretion efficiency), palatability, medication reviews with patients (and prevention of unnecessary polypharmacy), more informative and clearer labeling, elimination of unnecessary repeat prescriptions, improved coordination among prescriber, dispenser, and patient, and alternative treatments (exercise, physical therapy, diet, etc). The spectrum of options for gaining better alignment with sustainability is clearly vast. Numerous others involve design of APIs, drug formulation, and packaging. These factors and others have all been discussed in the publications of Daughton and Ruhoy, spanning the years 2003-2011, which have served as the basis for this report.

One of these approaches in particular has clear potential for immediate general implementation but does not receive sufficient attention - lower doses. Lower doses can translate into smaller dispensed quantities as well as reduced excretion of API residues. Lower doses can improve therapeutic outcomes for some patients and greatly reduce adverse drug events. The recommended doses for many medications may be too high for large segments of the population. Effective doses are often one-half of the recommended dose (or even lower) (Cohen 2003); table 9 of Cohen (2003) lists the reasons that drugs are often marketed with recommended doses that

can be unnecessarily too high. This is a very important but woefully under-researched aspect of pharmacology and one that has the potential to also quickly cut drug loadings in the environment significantly.

As pointed out in Ruhoy and Daughton (2008), high doses are often established for clinical trials to maximize the opportunity for achieving therapeutic endpoints; once marketed, the doses are not reevaluated or adjusted downward. Approaches for determining optimal, lower doses include personalized medicine (Daughton 2003b), which factors obvious variables such as gender-specific responses and less recognized practices such as chronobiology for ensuring maximally effective dosing schedules (Daughton and Ruhoy 2009b). The major roadblock is the time required on the part of physicians. Some insurers and healthcare providers have already begun to allow "pill splitting." But only certain medications (and restricted to particular formulations, e.g., tablets but not capsules) are amenable (Jain and Jain 2006).

The need for efforts focused toward better understanding the actions of medications is reflected in a statement attributed in 1999 (Cimons 1999) to Dr. Janet Woodcock, then director of the FDA's Center for Drug Evaluation and Research (CDER): "The sad truth is that, even after all the clinical development that occurs with every drug and even after drugs have been approved for a long time, we only have a crude idea of what they do in people... We don't really know why they work well in some people and not as well in others."

Note that at least one of the trends in the pharmaceutical development has served to also reduce overall doses. As first pointed out by Daughton (2003b), replacement of racemic drugs (equal mixtures of APIs that comprise optical isomers – or stereoisomers) with pure isomers (enantiomers) can reduce dose size. Optical isomers have identical molecular compositions but different 3-dimensional structures - which are mirror images of each other. The enantiomers can exhibit dramatically different physiological properties; sometimes, one enantiomer is responsible for the desired therapeutic effects, while its companion enantiomer may be ineffective or even responsible for side effects. Enantiopure drugs serve to directly cut therapeutic doses by at least one half (depending on how many optical isomers an API might comprise). This is a trend that has continued in pharmaceutical development, driven partly by the fact that one or more API enantiomers in racemic drugs might sometimes responsible for adverse drug reactions. Regardless of any pharmacological advantage that one enantiomer might have over another, enantiopure drugs hold the potential for resulting in the introduction of reduced quantities of APIs to the environment than do their racemic counterparts. This could result, for example, from the need for lower overall doses or because of more complete metabolism of one enantiomer to inactive products.

No single document has yet cataloged the extraordinarily broad array of actions, activities, and behaviors that determine and influence the entry of APIs into the environment. Some preliminary attempts at conceptualizing a comprehensive, integrated approach for reducing the entry of drugs to the environment have been made. One in particular is the actor modeling approach, which was first applied under the START project (Keil 2008; 2010; Titz and Döll 2009); actor modeling factors together all of the involved entities (e.g., manufacturers, stakeholders, healthcare professionals, consumers, etc.) and the processes they influence.

Green chemistry and other approaches to eco-efficient design can be applied to numerous aspects of a product's life cycle; these approaches, however, are not applied comprehensively to the life cycles of drugs. An ultimate challenge, for example, would be the design of drugs and the methods used for their delivery to minimize the excretion of unchanged APIs and bioactive metabolites. Much of the discussion in the US involving the application of green chemistry to pharmaceuticals has been led by the American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable (ACS 2005). Redesign of drugs is a topic already underway with respect to green chemistry. At the US FDA, it is being championed with respect to making drugs safer (Woodcock 2009). An overview of this topic is provided by Dunn et al. (2010).

But even in light of the numerous ways that the impact of drugs on the environment can be reduced, an emerging opinion is that these alone will not be sufficient in achieving truly sustainable use. Also required will be reductions in overall consumption. Reducing the usage of pharmaceuticals has long been excluded as a possible option. Extensive evidence exists, however, showing the numerous ways for how reduced usage could be achieved. The key to reducing consumption will be maintaining - or preferably improving - overall satisfaction and well-being for the healthcare consumer.

Unlike nearly all other consumer items, where approaches to sustainable consumption and usage might be obvious, what might constitute sustainable use of medications is not so easily articulated - especially for so-called "essential" drugs. Pharmaceuticals present one of the most daunting challenges with respect to sustainable use while at the same time maintaining or optimizing human health and ecological integrity. Innovative approaches are needed. Sustainable use of commodities usually involves two major approaches: better design and more efficient use (resulting in reduced consumption). Incentives for more efficient use are often oriented to encouraging altruism or self-interest (such as improved sense of well-being). It is difficult to currently see how this can be applied to medications - a commodity that is often begrudgingly purchased and whose actual consumption after purchased is often avoided; a prime example is the purchase of long-term maintenance medications for conditions having no overt signs (such as cholesterol levels), so the patient receives little gratification or feedback indicative of progress.

A better understanding of the nuances involved with consumer motivation for sustainability (and how it could be applied to the use of drugs) would be extremely useful. A recent article may provide some insights (see: Marchand et al. 2010).

If sustainability were used as a measure of success, it becomes clear that an overwrought focus on developing the best ways to dispose of unwanted drugs cannot succeed. By focusing on drug disposal, the prospects for sustainability could actually be made worse simply by increasing consumer purchasing of unneeded drugs since they are easy to dispose. The focus instead needs to be on ways to prevent the generation of unwanted drugs so that the need for disposal is minimized or eliminated. A focus directed toward an even more challenging goal would be how to design drugs and the methods used for their delivery to minimize the excretion of unchanged APIs and bioactive metabolites.

Formal recognition of the need for developing actions to reduce the incidence of leftover drugs rather than focus on waste disposal has only recently begun to emerge, as reflected by a

recommendation from the National Association of Boards of Pharmacy (NABP 2009b) that prevention measures should be pursued: "Recommendation 3: Work with Appropriate Entities to Research Methods that Reduce the Amount of Unused Medications."

One approach to reducing consumption would be to change the paradigm that has dictated the conventional physician-patient-drug relationship - where the orientation has long been on the drug itself, rather than on the therapeutic outcome actually desired. One far-ranging, but currently hypothetical, approach involves what might be called "just-right prescribing," where the patient would pay for services that succeed in achieving therapeutic outcomes, as opposed to paying for medications (regardless of their effectiveness). Applying "just-right prescribing" to healthcare, medication waste would be viewed as a prime metric of inefficient, non-optimal administration of health care. Redesign of healthcare using this perspective and the knowledge and expertise of medical practitioners, health-care administrators, pharmaceutical manufacturers, and environmental scientists could lead to a holistic system of balanced and optimally targeted delivery of medical care. Such a system could yield improved therapeutic outcomes, lowered costs, and reduced environmental impact.

Such an approach would necessitate further advancements in evidence-based medicine and personalized medicine. This concept is patterned after the practice called chemical management service (CMS), which is part of the larger concept of "material flow management service." This approach sells a service or the outcome desired from the use of a chemical - rather than the chemical itself. As first proposed in Daughton (2009) and Daughton and Ruhoy (2010), in applying the concept of CMS to healthcare, the ultimate objective would be the paradigm whereby medications are no longer sold or prescribed by themselves, but rather the desired therapeutic, lifestyle, or enhancement endpoint becomes the actual contract with the patient. This would serve to drive down the unnecessary and imprudent use of medications.

With hypothetical approaches aside, the specific topic of drug disposal and the more general topic of stewardship have fostered the involvement of several NGOs, such as the Product Stewardship Institute (PSI 2008a) and the Teleosis Institute. The Teleosis Institute was one of the early adopters of the Green Pharmacy concept, devoting an entire issue of its journal to the topic in 2007 (Teleosis Institute 2007).

The growing interest in sustainability and broader solutions to the drug waste problem is evident with the publication of the first books devoted to this topic:

"Green and Sustainable Pharmacy" (Kümmerer and Hempel 2010)
"Towards Sustainable Pharmaceuticals in a Healthy Society: MistraPharma Research" (Rudén et al. 2010)
"A Healthy Future - Pharmaceuticals in a Sustainable Society" (Bengtsson et al. 2009)

Other indicators of an emerging focus on sustainable use of pharmaceuticals include the introductory remarks of Sen. Kohl at the 30 June 2010 hearing on "Drug Waste and Disposal: When Prescriptions Become Poison" for the Senate's Special Committee on Aging (Special Committee on Aging (chaired by Senator Herb Kohl) 2010):

> "One of the best strategies to tackle the problem of drug disposal is to make sure drugs aren't wasted in the first place. We need to explore innovative ways to improve patient care and reduce waste through programs like medication therapy management, improved compliance, and patient education."

Finally, the emergence of legislation aimed at extended producer responsibility (EPR) to cover pharmaceuticals may help in developing more sustainable use (Blais and Maher 2010; Citizens Campaign for the Environment -Year Unknown (Possibly 2010); Maisel and Englebright 2010; Perry 2010; PPI 2010). EPR has been difficult to impose for pharmaceutical waste, as noted for Maine's act for proper disposal, which died in the State legislature on 26 March 2010 (Perry 2010).

A largely unrecognized benefit could emerge from the closer involvement of pharmaceutical manufacturers with drug waste. By using the data that could be mined from drug collections, manufacturers could gain insights they currently lack regarding the extent, scope, and magnitude of drug wastage. These data could be used to change manufacturing, packaging, and promotional practices - or to alter prescribing/dispensing practices. Insurers could use the data to determine optimal dispensing practices.

One embodiment of sustainable use of pharmaceuticals rarely discussed is the reclamation of APIs from wastes, ultimately for re-use or re-purposing - a process dubbed "drug mining" (Daughton 2003a). Such an approach might prove feasible for particularly costly drugs, such as certain chemotherapeutics. As proposed by the patent holder, reclamation could possibly be practiced in hospitals, where APIs could be mined from patients' excreta and other wastes (Pharmaceuticals.org 2008). Reclaiming APIs from wastes has historical precedence, such as the reuse of penicillin from soldiers' urine - a practice necessary during WWII when penicillin was in very short supply (Clarke 1979).

Eco-labeling

When measures are lacking for reducing drug usage or the generation of leftovers, one innovative approach pioneered in Sweden has involved the classification of APIs according to their potential for environmental impact - incorporating values for PBT: environmental persistence, bioaccumulation, and toxicity; with respect to bioaccumulation, note that the potential for biotransformation may be emerging as a better factor for predicting bioaccumulation than hydrophobicity (McLachlan et al. 2010). The objective of Sweden's classification/labeling program has been to guide prescribing so that certain drugs within given therapeutic classes can be preferentially prescribed - thereby limiting the entry to sewers of the least desirable APIs via either excretion or disposal. Several articles describe the development and status of this classification system (Gunnarsson and Wennmalm 2008; Stockholm City Council 2010a; b; Wennmalm 2009; Wennmalm et al. 2010; Wennmalm and Gunnarsson 2005; 2009; Wennmalm and Gunnarsson 2010).

The drugs recommended for common diseases as classified according to the environmental impact criteria of the Stockholm County Council are contained in a database - the "Wise List" (Stockholm City Council 2008; 2009; 2010b). In keeping with Sweden's labeling effort, the

implementation of so-called "eco-labeling" has also been discussed for personal care products (Klaschka et al. 2007).

Sweden's classification and eco-labeling effort could be extended to guide the responsible disposal of leftover, unwanted medications. By accommodating some other key parameters, such as disposal information tailored for each medication and safety information regarding the handling of waste, a labeling system could be devised that attempts to protect not just ecological integrity, but also human safety. The advantages of clear disposal guidance tailored to each drug is particularly attractive in several respects. First, certain drugs could probably be disposed to sewers with minimal potential for environmental impact, thereby obviating the need for alternative disposal mechanisms and also avoiding the increased potential for poisonings (from storage of leftovers awaiting disposal or from drugs disposed to unsecured trash); this avoids the current approach - which has caused considerable confusion and frustration - of "almost-one-size-fits-all" (that is, all except for certain exceptions). For example, some APIs are extensively excreted unchanged. For these, disposal to sewers adds only small incremental portions to ambient levels; this was first discussed by Daughton and Ruhoy (2009a). Second, exposure to certain APIs is extremely hazardous for certain sub-populations; these individuals must avoid handling these drugs during disposal (an otherwise avoidable hazard but one that has been introduced by current disposal guidance). Third, certain drugs are extremely toxic and can lead to single-dose fatalities. Storage for these drugs must be secured at all times (including leftovers discarded into trash); immediate disposal of these drugs might be preferably done by disposal to sewers. Currently, such useful information is lacking for the consumer (and sometimes even for the physician).

Biologics

Biologics comprise a broad and continually expanding class of pharmaceuticals whose chemical structures are based on proteins, nucleic acids, or sugars. They are used in vaccines, gene therapy, and other modalities not conducive to conventional "small molecule" APIs. These substances are often unstable in heat, light, and air, and generally unstable in the gut or inefficiently absorbed from the gut. In general, biologics do not pose the conventional concerns associated with small-molecule pharmaceutical disposal. Biologics also attract comparatively little attention from environmental scientists, as they pose considerably smaller environmental footprints than the more structurally stable synthetic APIs. Those that do get excreted - and even if surviving sewage treatment and environmental transformation or structural 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 their propensity for environmental degradation or denaturing by microorganisms, sunlight, and other physicochemical processes. An overview of biologics and the environment is provided by Kühler (2009).

No published evidence points to concerns that might be associated with disposal to sewers. On the other hand, disposing of biologics via the trash may pose unknown risks should someone unintentionally or unknowingly consume them orally or contact them with their skin, as the possibility of allergic reactions exists. Most biologics will be administered by healthcare professionals, since these drugs usually involve parenteral delivery routes. Exceptions include

the self-administered biologics used in long-term maintenance therapy (one example is the class of injectable TNF inhibitors, such as etanercept, which inhibit the production or recognition of tissue necrosis factor). Two scenarios would call for disposal. First would be expired product, usually in the form of some delivery device or container. The other is in the form of unused/wasted product (e.g., residues remaining in delivery devices, such as syringes). In neither case would flushing normally be considered a disposal option.

Legislative Activities

The last few years have witnessed an explosion of hearings and legislative involvement in several aspects of the drug disposal problem. The growing number of laws, regulations, and resolutions passed by city, state, and federal legislators has become very difficult to track. Legislation is in a constant state of evolution and is far too complex to cover here. Over 100 records currently exist in the DDS database that focus on legislation; but these represent only a fraction of the literature.

Given the wide range of legislative activities at the state and federal levels surrounding drug disposal, the United States Pharmacopeial (USP) Convention decided in 2010 to refrain from involvement in any standards-setting activities (USP 2010). A perspective from the law profession on federal regulations governing drug disposal was published by Morgan (2009).

A number of Congressional hearings involving various aspects of PPCPs have taken place over the last couple of years. The first Congressional hearing devoted to the topic of drug disposal was held in 2009 (US House of Representatives 2009). Another hearing was held on 30 June 2010 (Special Committee on Aging (chaired by Senator Herb Kohl) 2010). The Kohl hearing was covered in Erickson (2010b).

Congress has introduced a numbers of bills dealing with disposal, such as S. 3397 (Klobuchar et al. 2010); S. 3397 passed the Senate in August 2010.

Only 10 years ago was one of the first papers published that recognized the inconsistencies in how drug wastes are handled and regulated, as well as to bring some attention to the need for principles of stewardship (Rau et al. 2000). An excerpt from the section "Improve awareness and training":

> "The research community, EPA, FDA, and pharmaceutical manufacturers should work together to design educational programs to better inform investigators, healthcare providers, and patients about the potential environmental impacts of pharmaceutical use and appropriate disposal methods."

Some of the first legislation relevant to drug disposal focused on state statutes controlling the reuse of medications, for example within LTCFs. Perhaps the oldest legislation recognized as exacerbating the drug disposal problem is the Controlled Substances Act, which greatly complicates how collection events or returns programs can be run (US Department of Justice 1997). For in-depth discussion of the role played by the CSA in drug disposal, see Yeh (2010).

The first significant legislation intending to solve the consumer disposal problem was the State of Maine's S.P. 671 - L.D. 1826: “An Act to Encourage the Proper Disposal of Unused Pharmaceuticals” (State of Maine 2003). This act set the stage for the nation’s first state-wide mechanism for handling consumer leftover drugs - via an innovative mail-back program, coordinated with the state DEA and the USPS. This was followed by the first state law directed at mail backs (People of the State of Maine 2007).

A sampling of state statutes and bills pertaining to drug returns and reuse is available from various sources (CESAR 2008; NAMSDL 2009; 2010a; b; NCSL 2010b; PSI 2010). Several other references discuss the state of legislation and where the challenges reside (California DTSC 2010; Hubbard 2007a; Siler et al. 2008).

Various States have passed legislation that mandates the study of approaches for prudent drug disposal (e.g., Watson (sponsored by Donna Howard) 2009).

Although the initial forays into legislation have focused on consumer-level take backs and reuse, the latest efforts are beginning to focus on extended producer (corporate) responsibility (EPR) - where the manufacturers would take responsibility for collection of leftovers (Blais and Maher 2010; Citizens Campaign for the Environment -Year Unknown (Possibly 2010); Maisel and Englebright 2010; PPI 2010).

In 2009, the National Association of Counties (NACo), the country's largest local government organization, adopted a resolution supporting EPR for the collection of unwanted medicines: "Resolution in Support of a Safe, Convenient Medicine Return Program" (NACo 2009a; b).

Some states have also considered (or have passed) EPR legislation (Morrell et al. 2009; State of Maine 2010; State of Washington 2009).

In contrast to several other countries, legislation in the US that has focused on EPR has not been received favorably by the pharmaceutical manufacturing sector. The argument most frequently made against placing the responsibility for drug disposal on the drug industry is that healthcare costs for consumers would increase because of the need to raise drug prices to fund the EPR program. This argument, however, has not yet been successfully made in any peer reviewed study, and extremely little has been published to assess consumer acceptance of increased costs (e.g., Kotchen et al. 2009). In fact, the only existing data (namely, the existing EPR programs in other countries) argue otherwise. By implementing ERP programs and by mining the wealth of data that could be obtained from cataloging unused drugs, much could be learned about patient compliance, which in turn could prove invaluable in improving future drug design, formulation, and packaging. Such improvements could even serve to reduce the cost of medications in the long term.

Enforcement activities

Other than DEA actions involving controlled substances, legal or enforcement actions involving the disposal of medicinal pharmaceuticals have been exceedingly rare. Perhaps the first noteworthy case was in New York, where five healthcare facilities were directed to immediately

cease all discharges of pharmaceutical wastes into waterways within New York City's watershed. Noteworthy was that this enforcement action was not based on any known harm to the public but was instead justified on the basis of certain APIs, which, once treated as waste, were considered hazardous wastes (a practice that has long proved confusing and problematic for healthcare facilities nationwide) (Luxton and Walsh 2010; Office of the Attorney General 2010).

Worth noting here is that of the many APIs that are truly hazardous, only a few select APIs (fewer than 3 dozen) are actually explicitly captured under Resource Conservation and Recovery Act (RCRA) (i.e., as P- or U-listed chemicals); others, however, are implicitly covered if they display at least one of the characteristics of hazardous waste (i.e., ignitability, corrosivity, reactivity, or toxicity). Historically, this uneven classification has been an inevitable consequence of the introduction over the years of APIs with ever-increasing potencies and new targets for biological action. It is also a consequence of the problems associated with applying RCRA criteria to the unique dosage forms of APIs. OSHA's hazard classification of APIs with regard to occupational exposure is similarly uneven in its coverage. This is one of the reasons that chemotherapeutics, for example, have received comparatively little scrutiny with respect to workplace risks, despite posing considerable hazards. The intricacies and confusion surrounding drugs and RCRA are covered by Smith (2008).

Antibiotics and selection for antibiotic resistance

Although the focus of this report is not on the ways in which drugs disposed into the environment might have adverse impacts, antibiotics compose one particular class of drugs (other than controlled substances) that often stands out. The linkage between antibiotics and antibiotic resistance (AR) in bacteria is a multi-faceted issue - and one of keen interest with respect to human pathogens. The topic is far too complex to discuss here in a comprehensive manner; some of the many complexities underlying antibiotic resistance are summarized in Livermore (2003).

In the PPCPs bibliographic database, there are roughly 300 articles dealing with AR and the environment. With that said, it is important to recognize that a significant degree of naturally occurring resistance exists in the ambient (natural) environment. This is caused primarily by two factors: (1) continual "warfare" between microbes, many of which synthesize a broad spectrum of antibiotics to out-compete each other; of the bacteria that suffer substantial exposure, the survivors are conferred resistance, and (2) environmental stress is probably a common cause of development of antibiotic resistance; the types of general stress that can lead to resistance include changes or extremes in pH, osmolality, and temperature, among other stressors (McMahon et al. 2007). This natural level of AR then undergoes horizontal gene transfer - expanding the resistance across species. For these reasons, antibiotic resistance has always existed - long before the use of antibiotics by humans.

On top of this natural background level of exposure is that resulting from the prophylactic, therapeutic, and economic use of antibiotics for human, veterinary, agricultural, and aquaculture purposes. Larger quantities of antibiotics (but of fewer types) are probably used in agriculture (primarily CAFOs), but these have different routes to the environment. One additional source, little investigated in the US, is manufacturing waste streams (Larsson 2010; Larsson et al. 2007).

It is simply not possible to ascribe the spread of AR to any one cause - especially to the discarding of unused antibiotics. The presence of antibiotic-resistant bacteria in remote areas lacking overt sources of anthropogenic antibiotic usage demonstrates how confusing this topic can be (Sjölund et al. 2008).

While no one knows for sure the major contributors of AR as a result of human usage, it is generally acknowledged to be therapeutic and prophylactic use. During treatment, bacteria with AR are continually shed via excrement and washed from the surface of the body; AR bacteria occur on the skin because of antibiotics applied topically and because systemically administered antibiotics are excreted with sweat via the skin (Daughton and Ruhoy 2009a). These bacteria (or their AR genetic elements) can then survive sewage treatment. At this point, gene transfer can occur or humans/wildlife can be directly exposed to the AR bacteria. Resistance to one antibiotic typically confers resistance to others (as the mechanism of resistance is often evolutionarily conserved across genera). This is why multi-drug resistance is so common.

Antibiotics can be concentrated by several orders of magnitude in biosolids. Subsequent use on land could serve to select for future AR. A very under-appreciated mechanism by which AR can evolve is from exposure to substances that are not generally recognized as antibiotics. This is done by a variety of mechanisms, including induction of over-expression of efflux-pumps, metabolic routes, or other means. In fact, treatment with one antibiotic may result in development of AR for other, unrelated antibiotics but perhaps not for the actual antibiotic involved with the exposure. This is perhaps a major route by which resistance can develop from exposure to low levels of antibiotics (e.g., see: Kohanski et al. 2010).

Finally, the disposal of antibiotics by flushing into sewers could theoretically introduce transient spikes in antibiotic levels entering STPs, which might be sufficient to select for AR; but this has not yet been reported. Flushing into septic systems could hypothetically result in the same outcome, but the more likely outcome would be severe disruption of the septic system because of mass die-offs of certain species or disruptions of the resident bacterial communities.

The occurrence of antibiotic resistant bacteria in any number of myriad environmental compartments is often ascribed to disposal of leftover medications without any supporting evidence. This leads to further confusion by those outside the field. A case in point is evident in Roach (2010).

CONCLUDING ANALYSIS

No direct evidence links drugs disposed to sewers with increased levels of active pharmaceutical ingredients (APIs) in the ambient environment. Assertions that disposal of leftover drugs to sewers contributes measurably to environmental residues of APIs are based almost completely on logical, but still unproven, assumptions.

In the absence of scientific data, the dominant drivers for developing state or national guidance for consumer disposal of leftover medications should not be based solely on assumptions

regarding adverse environmental impacts. This is not only misguided, but by placing the focus on the symptoms of the problem (leftover, unwanted drugs), the consumer's attention is diverted away from the actions required for curing and preventing the actual problem. The focus instead needs to be placed on preventing waste rather than on disposing of the waste. Furthermore, guidance designed to alter consumer behavior in the disposal of unwanted drugs could possibly have unanticipated, adverse consequences when not developed from a holistic consideration of the complex interplay of the myriad positive and negative feedback circuits involved with prescribing, dispensing, and consumption of pharmaceuticals.

There appear to be innumerable points along the life cycle of a drug (spanning manufacture to ultimate usage) where redesign or improvements could yield profound changes in the types and quantities of APIs used. These changes could result in reduced usage or in usage having reduced potential for environmental impact. Many of the myriad actions required to minimize the incidence of leftover drugs happen to result in reduced consumption of medication. This in turn results in reduced excretion of APIs. For consumer drugs, excretion is the primary origin of API residues in the environment; manufacturing and agricultural uses (such as confined animal feeding operations) may serve as other significant sources in certain locales, but these are issues unrelated to consumer use. This means that the objective of reducing the entry of human-use APIs to the environment is primarily accomplished indirectly by collaborating in the development or redesign of policies and actions of the healthcare communities regarding the usage of medications.

In-depth examination of the published literature reveals that the very same changes in the actions, activities, behaviors, and customs practiced in the administrative of healthcare (and veterinary care), and which are required for reducing the entry of APIs to the environment (by reducing excretion and disposal), can have profound collateral outcomes, extending far beyond any original intent of protecting the environment. These major outcomes could include improvements in many aspects of healthcare, including: therapeutic outcomes, and reductions in: (i) healthcare costs, (ii) morbidity and mortality from unintentional poisonings, (iii) diversion (and its associated crime) and abuse, (iv) unnecessary and imprudent donation of drugs (particularly during humanitarian relief efforts), and (v) unanticipated mass poisonings of wildlife.

This examination points to the wide spectrum of benefits that could potentially ensue from establishing transdisciplinary collaborations among the various healthcare and veterinary communities, pharmaceutical and pharmacy industries, health insurance industry, water utilities, regulators, environmental scientists, and numerous stakeholders and beneficiaries - with participation of processionals from disparate fields, such as engineering, science, healthcare, veterinary science, sociology, psychology, pharmacology, toxicology, pharmacy, health insuring, and criminology.

With a concerted focus on solutions aimed at reducing waste instead of disposing of waste, a healthcare system could evolve that is more effective, efficient, and environmentally sustainable.

SUGGESTED FOR FUTURE CONSIDERATION

After an in-depth evaluation of the many facets of the drug disposal issue, it is clear that a very wide range of actions could be considered for reducing the incidence of accumulation of leftover drugs and the consequent need for disposal while also improving the quality of healthcare. Many of these have been discussed in the articles that formed the basis for this report; others are covered in the articles that compose the DDS database. Several ideas that are rarely ever discussed, however, are captured below.

(1) **Enlist the public to better track and understand the types and quantities of medications that go unused**. It is clear that a better understanding of the types and quantities of medications that go unused would be extremely useful. It is also clear that considerable expense, time, and obstacles are faced in obtaining inventories of leftover drugs (either those stored in homes or collected during take-backs). Alternative means of collecting these data would be extremely beneficial for improving prescribing and dispensing practices as well as for reducing environmental impact.

An unexplored way to mine data from the public regarding leftover drugs would be to create a publicly accessible Internet database where individuals can log the quantities and types of their leftover drugs, together with whatever other types of additional data might be useful to investigators, such as the reasons for the wastage, the method of disposal (or storage), and the geographic locale. Although there would be obvious quality control issues (such as ensuring truthful and accurate data), precedence exists for the potential utility of this approach. One existing example is on-line database that catalogs self-treatment of autism - operated as the Interactive Autism Network (IAN 2010). Applied to leftover drugs, this approach has extraordinary potential for providing insights on a host of issues involving the relationships and inefficiencies in the manufacturer-physician-patient chain. Such data could lead to new ways to select optimal medications and to prescribe and dispense medications in optimal quantities; it could also reveal significant geographic differences.

Furthermore, the mere act of a patient being able to enter the types and quantities of leftover medications into a publicly accessible database (and to be able to see the data entered by others) may alter their behavior and attitude toward future purchases of medications - making them more cognizant of over-purchase, unnecessary purchase, and wastage.

(2) **Centralized database for data mined from collected medications**. As suggested above for patients, drug collection programs having the resources to mine data from returned drugs could log the collected data into a central database. These data could then be used by manufacturers, prescribers, and dispensers to modify their practices so that leftovers are continually reduced. Pollution prevention efforts involving prescribing and dispensing could then focus on targeting those medications that: (i) are costly, (ii) have high abuse potential, (iii) are acutely toxic (e.g., single doses that can be lethal), (iv) have poor compliance resulting from patients' inability to perceive the need to continue with treatment regimens, or (v) have been shown to otherwise be extensively metabolized (and therefore poorly excreted) and therefore have higher potential for environmental harm if disposed.

A pre-existing program based in Texas that collects consumer self-reported data regarding leftover medications might serve as an example for how a nationwide database might be designed: "Unused and Expired Medicines Registry (UEMR)" (Community Medical Foundation for Patient Safety -Year Unknown; Mireles 2005; 2006).

(3) **Other uses for data mined from collection of leftover drugs.** One aspect of drug-returns data has rarely ever been capitalized on. By determining which drugs are returned (e.g., in take-backs) most frequently or in the greatest quantities, decisions can be better informed as to which APIs to select for targeting in local environmental monitoring studies. One example of the type of data that could prove useful is reported by James et al. (2009), in Table 1 of which is presented the top 20 medications returned during a collection event in New Zealand. Depending on their pharmacokinetics, these drugs would contain the APIs having a high probability of being excreted into sewers. By focusing on those that are normally extensively metabolized (resulting in little excretion), those APIs in the ambient environment having significant contributions from disposal could possibly be identified. Significant variations could occur across geographic locales, as first noted in Daughton (2003b). Geographic variabilities are known to occur in prescribing, as exemplified in a recent study of Medicare spending on drug purchases (Zhang et al. 2010). This study found large variations in expenditures across hospital regions. Contributors to these discrepancies were variations in the specific drugs that were prescribed as well as the number of prescriptions filled.

(4) **Explore the feasibility of deposit-refund systems.** The handling and disposition of drug waste has always differed markedly from the approaches used for other wastes. One aspect never considered for drug waste is deposit-refund schemes, such as long-used for glass bottles and aluminum cans. Deposit-refunds could be particularly attractive for drug delivery devices or for the growing numbers of new sophisticated containers - one example being the NextBottle (One World DMG 2010). As these devices become more sophisticated and costly (such as with the integration of electronics or design of multi-function containers), recycling, reusing, or re-purposing will become more viable. With a deposit-refund system implemented through pharmacies, additional opportunities for pharmacist counseling would arise, possibly serving to improve patient compliance. Deposit-refunds for medications have rarely ever been discussed, however, one example being Polimeni (2008).

An example of one major class of commonly used devices is Orally Inhaled and Nasal Drug Products (OINDP). OINDP devices (such as inhalers) could eventually pose special challenges - especially once electronics become an integral part of the device. Perhaps the best stewardship model for OINDPs could be the electronics industry, where the used product would be returned to the manufacturer, who would then disassemble the device and reclaim the constituents or detoxify them.

GLOSSARY

ADE: adverse drug event
ADR: adverse drug reaction
APIs: active pharmaceutical ingredients
AR: antibiotic resistance
ASCP: American Society of Consultant Pharmacists
ATC: Anatomical Therapeutic Chemical Classification System
CAFOs: confined animal feeding operations
CASA: National Center on Addiction and Substance Abuse (Columbia University)
CDER: Center for Drug Evaluation and Research
CIWMB: California Integrated Waste Management Board
CMS: chemical management service
CPSC: U.S. Consumer Product Safety Commission
CRCs: child-resistant closures
CSA: Controlled Substances Act
CVM: Center for Veterinary Medicine (FDA)
DDS: literature bibliographic database on leftover drugs, drug disposal, and environmental stewardship
DEA: Drug Enforcement Administration
DoD: Department of Defense
DOJ: Department of Justice
DOOP: disposal of old pharmaceuticals
DOT: Department of Transportation
DRIs: degradation-related impurities
DTC: direct-to-consumer (advertising)
DUMP: dispose unwanted medicines properly
EHRs: electronic health care records
EPA: Environmental Protection Agency
EPR: extended producer (corporate) responsibility
FDA: Food and Drug Administration
FMEs: fatal medication errors
FTC: Federal Trade Commission
HHS: Health and Human Services
HIOs: health information organizations
HIPAA: Health Insurance Portability and Accountability Act
HPAPIs: highly potent active pharmaceutical ingredients
IARC: International Agency for Research on Cancer
LCSA: life cycle sustainability analysis
LTCFs: long-term care facilities
MDIs: metered-dose inhalers
MNU: les Medicaments Non Utilises (unused medicines)
MRP: Medications Return Program (British Columbia, Canada)
MURs: medication use reviews
NABP: National Association of Boards of Pharmacy
NABP: National Association of Boards of Pharmacy
NaCO: National Association of Counties
NACWA: National Association of Clean Water Agencies
NADDI: National Association of Drug Diversion Investigators
NAMSDL: National Alliance for Model State Drug Laws
NAO: National Audit Office (London)
NAPRA: National Association of Pharmacy Regulatory Authorities (Canada)
NCPIE: National Council on Patient Information and Education
NCSL: National Conference of State Legislatures
NIOSH: National Institute for Occupational Safety and Health
NRDC: National Resources Defense Council
NSAIDs: non-steroidal anti-inflammatories
OIG: Office of Inspector General
OINDP: orally inhaled and nasal drug products
ONDCP: Office of National Drug Control Policy (Executive Office of the President)
ORD: Office of Research and Development (US EPA)
OSHA: Occupational Safety and Health Administration
OTC: over-the-counter
PBT: persistence, bioaccumulation, and toxicity
PCPSA: Post-Consumer Pharmaceutical Stewardship Association (British Columbia, Canada)
PDMA: Prescription Drug Marketing Act
PDMPs: prescription drug monitoring programs
PhRMA: Pharmaceutical Research and Manufacturers of America
PI: prescriber-identifiable data
PK: pharmacokinetics
PoM: prescription-only medicines
PPCPs: pharmaceuticals and personal care products
ppt: parts-per-trillion (ng/L)
PRN: "as the situation arises" or "as needed"
PSF: Pharmaciens sans Frontières (PSF) [Pharmacists Without Borders]
PSI: Product Stewardship Institute
RCRA: Resource Conservation and Recovery Act
REMS: Risk Evaluation and Mitigation Strategy
RUM: Return Unwanted Medicine
SLEP: Shelf-Life Extension Program
SMDME: Safe Medicine Disposal for ME program
SNS: Strategic National Stockpile
STP: sewage treatment plants
TDS: transdermal and topical drug delivery systems
TNF: tissue necrosis factor
UEMs: unused and expired medications
USNER: National Euthanasia Registry (Protecting Veterinarians)
USP: United States Pharmacopeia
USPS: U.S. Postal Service
VA: U.S. Department of Veterans Affairs
VIPPS: Verified Internet Pharmacy Practice Sites
WHO: World Health Organization

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ILLUSTRATIONS PERTINENT TO DRUG DISPOSAL AND STEWARDSHIP (PREPARED DURING THIS PROJECT)

Following in this section are illustrations prepared during the course of this project that are relevant to drug disposal and stewardship. Most of these have been published in the peer-reviewed literature, as cited here (in the order following):

Daughton CG. "The Environmental Life Cycle of Pharmaceuticals [illustration published in: Daughton CG "Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure," In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, San Diego: Academic Press; **2008**, pp. 66-102]," US EPA, Las Vegas, NV, December 2006; available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf.

Daughton CG "Illicit Drugs and the Environment [illustration published in: Daughton CG "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology," *Reviews of Environmental Contamination and Toxicology*, in press, March **2011**)], US EPA, Las Vegas, Nevada, 7 December 2009 (rev 17 June 2010).

Daughton CG. "Accumulation and Disposal of Pharmaceuticals [illustration published in: Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environment International*, **2008**, 34(8):1157-1169]," US EPA, Las Vegas, NV, 10 May 2008.

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Ruhoy IS and Daughton CG "Disposal as a Source of Pharmaceuticals in the Environment," U.S. EPA, Las Vegas, NV; illustrated poster, December **2007**; NERL-LV-ESD-07-129; available: http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-1.pdf

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Environmental Life-Cycle of Pharmaceuticals

created by CG Daughton
US EPA, Las Vegas
2 December 2006

transformation/degradation

mineralization

stewardship opportunities

Manufacturer

Commerce distribution

Wholesalers Distributors

Agriculture (e.g., orchards)

runoff

excrement

pets

euthanized carcasses

potential for acute/chronic poisoning of wildlife scavengers

carcasses of medicated animals

airborne dusts (e.g., medicated feed)

occupational human pulmonary exposure

physician samples

Physicians

Feedstores

Vet use

domestic animals

prescribing

unsold product

Reverse distributors

dispensing pharmacies Rx & OTC

CAFOs

Aquaculture

waste residuals pretreatment

humanitarian donations: excess or unusable leftovers

sloughing of antibiotic-resistant bacteria/genes

Waste Treatment (e.g., lagoons)

manure solids

Soil amendment/ disposal

atmospheric release (e.g., anaesthetics)

Human consumer use

Gene Exchange multi-drug resistance

naturally occurring bacteria

exposure to resistant bacteria

Take-Backs, Mail-Backs, Collection events

Incineration

unused/expired leftovers

LTCFs Hospitals Hospice

Leftover medications

Stored awaiting disposal

Diversion Abuse (e.g., pharming)

acute poisonings: accidental & purposeful

diversion by gleaners

Landfill

trash

RCRA Hazardous Waste

release of dermal products from bathing

excretion from oral & parenteral use

Disposal by consumer

trash

Incineration

Waste Treatment

toilet

groundwater (artificial recharge, colloidal transport)

Aquatic exposure

toilet or sewerage

Disposal by Coroner's

research of Ruhoy 2006

optional

Law enforcement (controlled substances)

Wildlife exposure (scavengers)

sediments (sorption)

straightpiping & overflow events

runoff

leachates

landfill

Plant-Made Pharmaceuticals (PMPs)

Molecular Pharming

finished drinking water treatment

receiving waters

Waste Treatment

Sludge Biosolids

Soil Amendment

groundwater

"toilet-to-tap"

drug residues & transformation by-products

Recreation

Advanced Treatment (recycling)

aqueous effluent

irrigation

PMPs cross-contaminating food supply

Wildlife exposure from grazing/ foraging

Chronic, Low-Level, Incidental Human Exposure

Oral & Dermal

uptake by plants & crops

uptake by soil-dwelling organisms

Illicit Drugs in the Environment

created by CG Daughton
US EPA, Las Vegas
7 December 2009
(revised 17 June 2010)

Medical Prescribing
Manufacturer Distributor
Including Over-Prescribing
Doctor Shopping
Hospital Shopping
Dispensing Pharmacies
LTCFs
Hospitals
Hospice
Patients
Drug Trafficking; Clan Labs
Illegal "Prescribing"
Diversion & Pharming
Law Enforcement Seizures
Incineration
Banknote Contamination
Chronic, Ultra-Low-Level, Incidental Pulmonary Exposure
Products of Incomplete Combustion
Airborne Aerosols
Atmospheric Release
Desired Drug plus Adulterants and Impurities
Smoking & Dusts
trash
Unused/Expired Leftovers
Human medical use
Human recreational use & abuse
Used Medical Devices/Patches
Acute Poisonings: Accidental & Preventable
Contamination of Surrounding Surfaces
Urine & Feces
Dermal Transfer
Landfill
FEUDS: Forensic Epidemiology Using Drugs in Sewage
Leachate
Toilet or Sewerage [parent drug, metabolite, conjugate]
Release during Bathing
Excretion via Sweat
Excretion after Oral & Parenteral Use
Urine & Feces
Sludge Biosolids
Waste Treatment
Straightpiping & Overflow Events
Sediments (sorption)
Aquatic exposure
Soil Amendment
Aqueous Effluent
Receiving Waters
Veterinary Use: Designer Drugs & Analogs
Clan Labs
Runoff
Recycling
Animal Racing
Fishing
CAFOs
Site Remediation (including homes)
Advanced Treatment
Drug Residues & Transformation By-Products
Chronic, Low-Level, Incidental Human Exposure
Food
Food
Aquaculture
Exposures via Contaminated Sites
Finished Drinking Water

Accumulation and Disposal of Pharmaceuticals

IS Ruhoy & CG Daughton
U.S. EPA-Las Vegas
15 December 2006
(rev 10 May 2008)

Cemeteries/Crematoria
Coroner
see: Ruhoy & Daughton 2007
Decedent
Unusable Donations
Cruise Ship Pharmacies
Prisons
In-Patient
Abandoned
Clan Labs
marine discharge
Donations
Out-Patient Clinics Nurses Offices
Internet
Consumer
Medicine Cabinet
Abusers (e.g., "pharming")
Manufacturers
Pharmacies
Confiscation (e.g., border check points)
Take-Backs & Collection Events
Schools
Black Market
Drug Sharing
Dentists
Controlled Susbtances
Controlled Substances
Reverse Distributors
Physicians
Physician Samples
Law Enforcement
Diversion
Illegal
Transporter
Hospitals
Pharmaceutical Representatives
In-practice Use
Via Pets
Military
Hospice
Veterinarians
LTCFs
Distributors
CAFOs
Ambulances Fire Stations
Vendors
First Aid Kits
Agriculture (farmers)
Zoos

Points of Accumulation & Disposal
Discard to sewerage
Discard to trash/landfill
Incineration

Factors Influencing Drug Consumption

created by CG Daughton & IS Ruhoy
US EPA, Las Vegas
8 December 2007 (rev 28 April 2008)

Pharmaceutical Sales Representatives
- Detailing
- Sampling

Promotionals

Manufacturers Distributors
- Educational meetings & events for physicians
- CME linked to marketing
- Medical journal advertising
- e-Sampling e-Vouchers
- Virtual Detailing

Reduces Prescribing

Counteracting Promotions
- Counterdetailing
- Point-of-care dispensing
- Consumer education
- Physician education
- P4P: Pay for Performance
- Restrictive formularies
- Evidence-based medicine

Prescribing
- Drugs prescribed based on patient requests
- Drugs prescribed as "prn"
- Drugs with complicated instructions
- Off-label prescribing
- Drugs prescribed to treat side effects
- Patient hand-offs (hospitals)
- Changes in treatment
- Lack of knowledge

Dispensing
- BTC drug expansion (behind-the-counter)
- Non-standardized labels
- Prescribing pharmacists (point-of-care)
- Free/low-cost medications
- Extended quantities (insurance)

Increased Consumer Acquisition
- Internet patient forums (sharing misinformation)
- Inaccessible, unused residues in containers & patches
- Abandoned & lost drugs
- Purchase of excessive quantities of OTC drugs
- Doctor Shopping Polypharmacy
- Internet and grey-market availability
- Increased marketing of human drugs for pets
- DTC Advertising
- Rx-to-OTC Switches

Non-adherence Non-compliance
- Disease state (dementia, depression. etc.) Death
- Inappropriate & unusable charitable contributions
- Poor perception of disease severity; imagined improvement
- Drugs with complicated delivery systems
- Complicated treatment regimes
- Patient confusion; lack of incentive
- Ineffective
- Adverse Drug Reactions (ADRs)
- Psychosocial factors
- Stockpiling for future use
- Sensory aversion
- Deliberate under-dosing

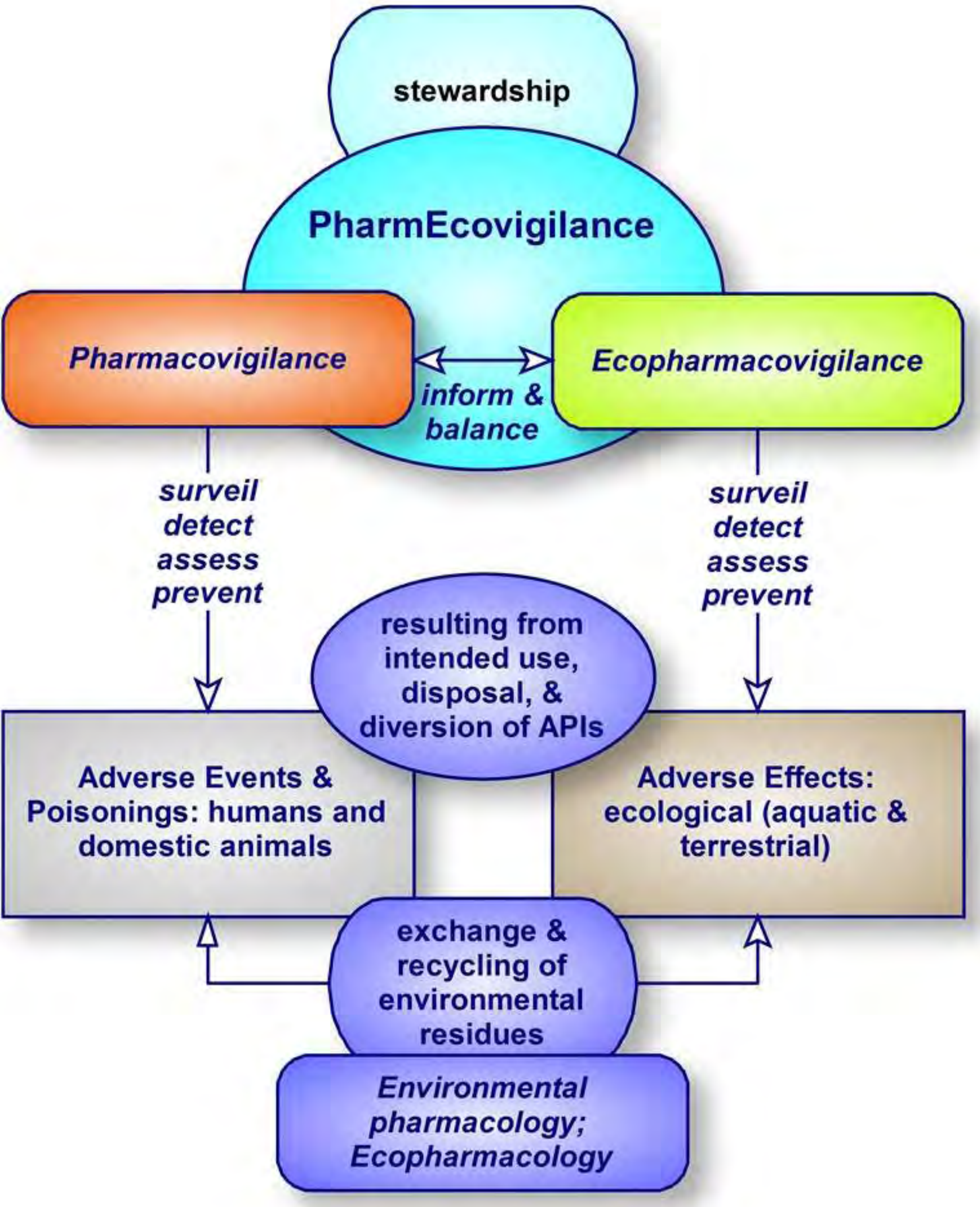
Increased Consumer Wastage

Illicit drugs

Reduces Usage & Wastage
- "Concordance"
- Small-quantity trials
- Installment dispensing
- Medication resuse
- Abuse & addiction prevention

Role of PharmEcovigilance: Minimizing Human & Ecological Impacts

created by CG Daughton
US EPA, Las Vegas
16 April 2008



Unintentional, Unanticipated Exposure to Drugs

created by CG Daughton & IS Ruhoy
US EPA, Las Vegas
8 December 2007 (rev 4 June 2008)

Prescribing (both human and veterinary drugs)

Dispensing

Factors increasing drug use or wastage

- purchasing
- prescribing
- dispensing
- availability
- marketing & promotionals
- patient non-compliance

Patient

Consumer Wastage (leftover, unused)

Abuse. Addiction. Sharing.

Diversion

Disposal via trash

Landfills Incineration

Excretion & Bathing

Disposal via sewer drains

Leachate

Exposed Public

- unapproved exposure
- unexpected exposure
- no consent for exposure
- unable to decline exposure
- chronic, indefinite exposure
- unknown potential for effects

API-Tainted Foods

API-Tainted Water

Agricultural soil amendment

Irrigation

Biosolids Recycled water

Rivers Lakes Oceans

Treatment

Sewage

Chemical Stressors

availability
purchasing
marketing & promotionals
Factors increasing drug use
prescribing
dispensing

Medical Use

Excretion & Bathing

wastage (leftover, unused)

Disposal

Source

Diminished Function (e.g., disease)

Effects:
adverse
therapeutic
none

molecular
cellular
organ
organism

Environmental pollution

Transport / Transformation

Biological Effect

Medical Use

air
water
diet
soil/dust

dilution
dispersion
distribution
partitioning

mass absorbed
metabolism
target site

Chemical Characterization

Dose

chemical analysis
identification
quantitation
monitoring

pathway
route
timing
duration
frequency
magnitude

Biological Exposure

Traditional domain of Pharmacovigilance

Additional domain for PharmEcovigilance

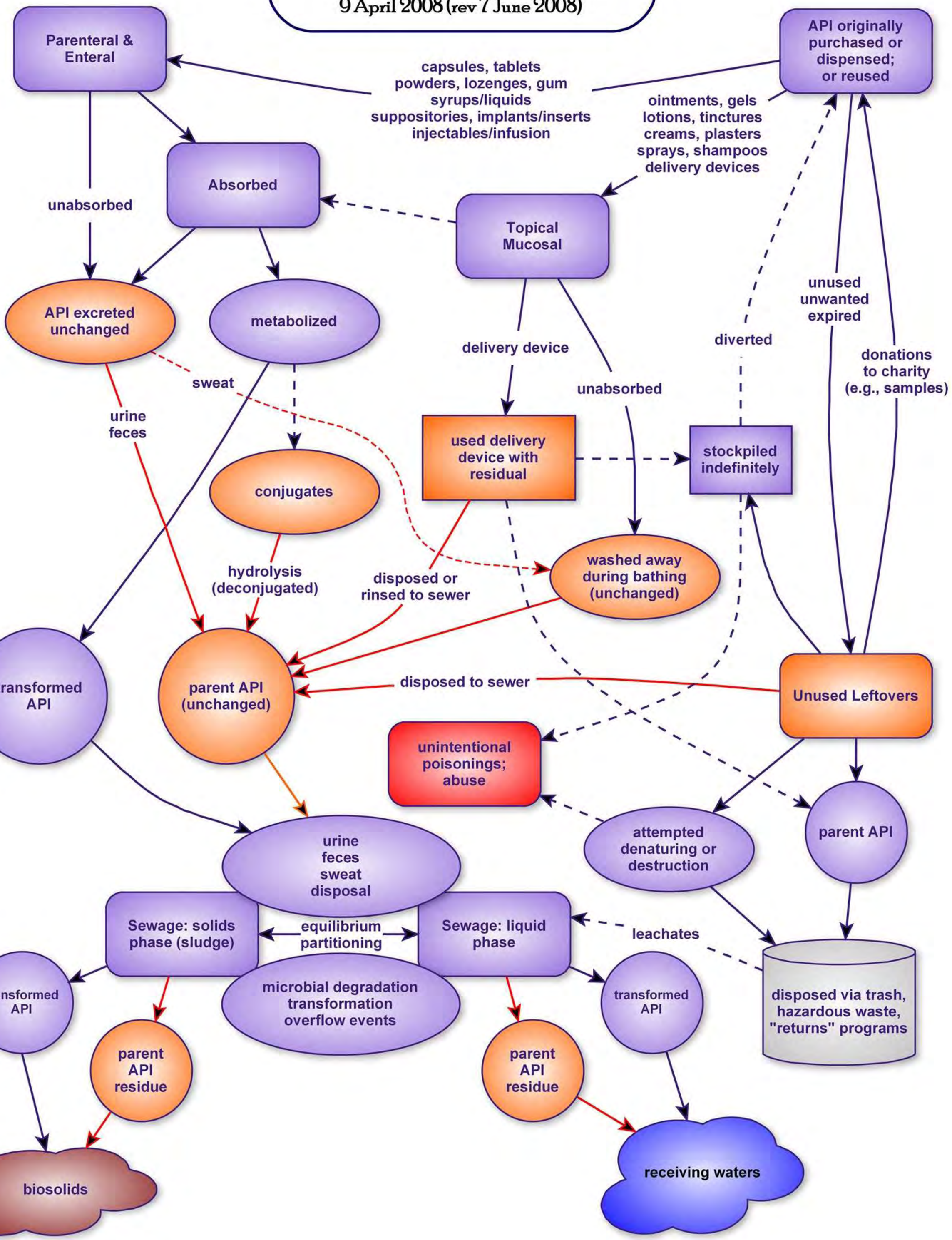
Environmental Risk Paradigm

PharmEcovigilance and Environmental Risk

created by CG Daughton & I Ruhoy
US EPA, Las Vegas
4 November 2007

PharmEcokinetics of APIs

created by CG Daughton & IS Ruhoy
US EPA, Las Vegas
9 April 2008 (rev 7 June 2008)

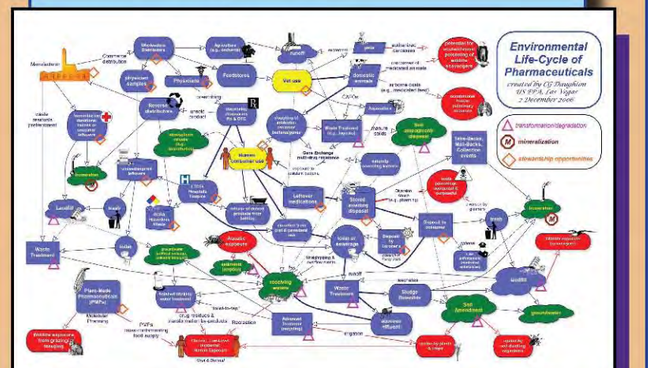


Pharmaceutical Disposal and the Environment

Ilene S. Ruhoy, MD and Christian G. Daughton, PhD

U.S. EPA, Office of Research and Development, National Exposure Research Laboratory, Environmental Sciences Division, P.O. Box 93478, Las Vegas, Nevada 89193-3478

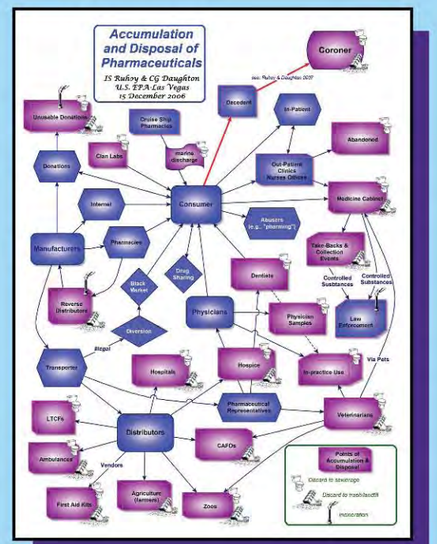
Pharmaceuticals can contaminate the environment via a complex network of sources and pathways.



Pharmaceuticals have myriads of uses for both humans and animals (see: *yellow nodes*), including therapy, disease prevention, diagnosis, cosmetics, and lifestyle. Hundreds of widely used active pharmaceutical ingredients (APIs) can gain entry to the environment from numerous locations in society (*green nodes*), primarily as a result of their intended use – as caused by excretion or bathing. Disposal of unwanted, leftover medications to sewage and trash is another source of entry, but its relative significance is unknown. As ultra-trace pollutants, wildlife and humans

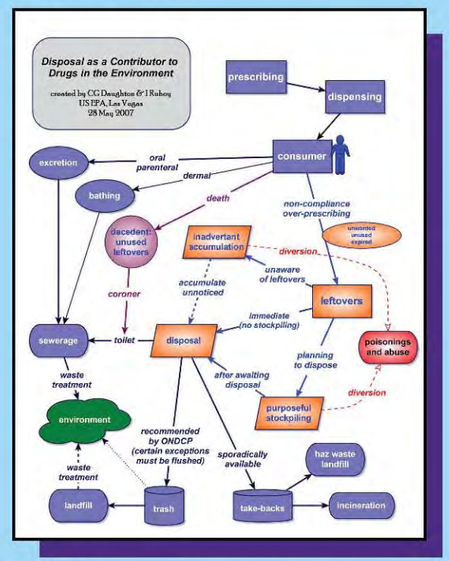
can experience long-term exposure to APIs via contaminated water and foods (*red nodes*).

Leftover, unwanted pharmaceuticals can accumulate at many locations.



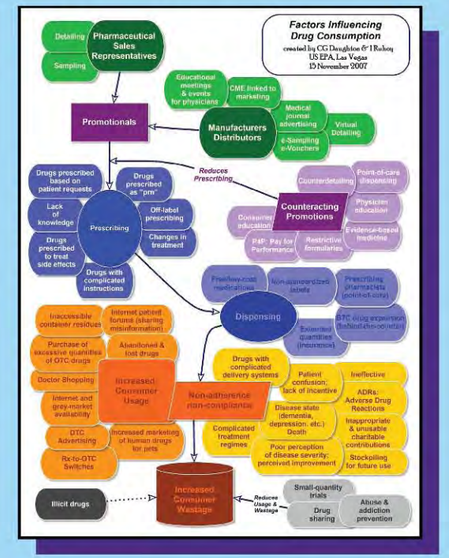
At numerous locations, unwanted pharmaceuticals are stored and eventually disposed by various means of collection or by discarding directly into sewerage or trash. Collected, leftover medications are generally disposed at landfills or by incineration.

Disposal of consumer medications can occur after leftover drugs are set aside or stored.



Leftover drugs tend to accumulate. These unwanted medications are intentionally (or unknowingly) stored prior to a decision to dispose of them. During storage, a leftover drug can be diverted to those for whom the medication was never intended. This can lead to poisoning of humans and pets, or to abuse and addiction.

Many factors cause medications to remain unused, creating leftover drugs that accumulate.



A wide spectrum of forces underlies the generation of leftover drugs, ranging from certain practices of manufacturers, distributors, prescribers, dispensers, and patients themselves. Much of the need for drug disposal could be eliminated by focusing corrective actions on these major causes.

Products

Ruhoy, I.S. and Daughton, C.G. "Types and Quantities of Leftover Drugs Entering the Environment via Disposal to Sewage - Revealed by Coroner Records," *Sci. Total Environ.*, **2007**, 388(1-3):137-148.

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available from: http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-2.pdf

Disposal as a Source of Pharmaceuticals in the Environment

Ilene S. Ruhoy, MD and Christian G. Daughton, PhD

U.S. EPA, Office of Research and Development, National Exposure Research Laboratory, Environmental Sciences Division, P.O. Box 93478, Las Vegas, Nevada 89193-3478

Introduction

Active pharmaceutical ingredients (APIs) from a large and diverse spectrum of pharmaceuticals can enter the environment as trace contaminants, especially in waters, at individual concentrations generally less than a part per billion (µg/L) but sometimes more. These trace residues may pose risks for aquatic life and cause concern with regard to human exposure, such as in drinking water supplies.

The predominate route by which APIs gain entry to the environment is via the discharge of raw and treated sewage contaminated with APIs as a result of their intended use in therapy or for lifestyle/cosmetic purposes.

Residues of APIs from parenteral and enteral drugs are excreted in feces and urine, and topically applied medications (plus APIs excreted in perspiration) are washed from skin during bathing.

For most APIs, the fraction of unchanged, parent API transferred to the environment is attenuated as a result of metabolic alteration in the body or transformation within a sewage treatment facility. For some APIs, only a small percentage of the total amount used is ever transported to the environment.

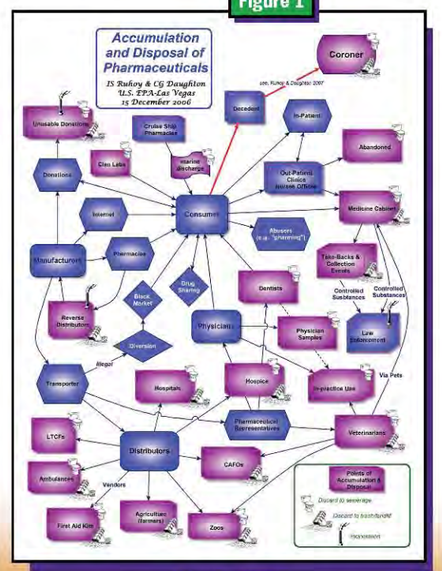
A secondary route of transfer of APIs to the environment is from the purposeful, direct disposal of medications to sewers and trash. The relative significance of this type of disposal with respect to excretion and bathing is poorly understood and subject to speculation. **Two major aspects of uncertainty exist. First, it is unknown what percentage of any particular API in the environment originates from disposal; the individual percentages probably vary dramatically among APIs. Second, disposal undoubtedly occurs from a variety of largely uncharacterized sources.**

Sources of disposal, along with the types and quantities of APIs resulting from each source, are important to understand so that effective pollution prevention approaches can be designed and implemented.

The accumulation of leftover, unwanted drugs can be used as an indicator of three major conditions:

1) Leftover drugs, when disposed to sewage or trash, represent a diverse source of potential chemical stressors in the environment.
2) Accumulated drugs represent increased potential for drug diversion, with its attendant accidental poisonings and purposeful addictive usage.
3) Leftover drugs represent wasted healthcare resources and lost opportunities for medical treatment.

Figure 1



27 November 2007

Objectives

Summarized here is a project whose objectives were to:

- Catalog the diversity of locations where drugs are used and accumulate, eventually requiring disposal.
- Define the processes that control and drive the consumption, accumulation, and disposal of human pharmaceuticals.
- Identify opportunities for pollution prevention and source reduction.
- Develop an approach for accurately identifying the APIs (and their actual quantities) being disposed.

Accomplishments

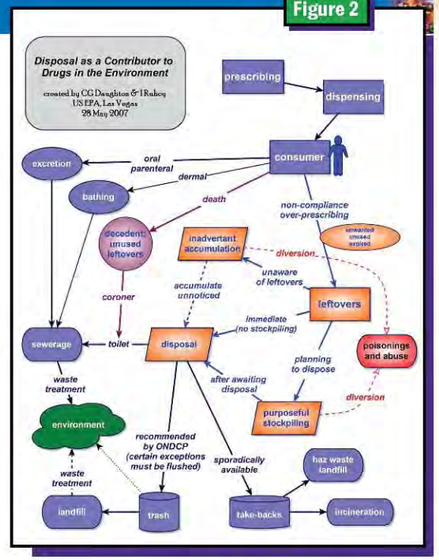
Identification of Sources: Probably more than for any other perishable, nonfood item consumed by humans, medications are used and stored at a vast array of locations throughout society. These products are frequently purchased in excess or not fully consumed as directed (e.g., patient non-compliance), leading to the accumulation of unwanted, leftover drugs. A broad spectrum of locations at which drugs are used and can accumulate, eventually leading to disposal, are shown in Figure 1. The relative significance of each of these sources with respect to disposal is currently unknown.

Factors Governing Disposal: The processes leading to the disposal of drugs by the individual consumer are illustrated in Figure 2. A significant point is that accumulated, leftover medications pose several major problems for human health and safety and for the integrity of the environment. These problems result from the diversion of accumulated drugs to those for whom they were not intended (leading to accidental and purposeful poisonings of infants, children, adults, and pets) and from the disposal of accumulated drugs to trash and sewage. The latter promotes the entry of APIs to the ambient environment.

Factors Governing Consumption and Accumulation: Numerous factors affect the consumption of drugs by consumers (Figure 3). Most serve to increase use, although several are at work to reduce use. Most of these factors are amenable to measures that could be designed to reduce their influence on the consumer. But these measures, in general, are outside the purview of the EPA. The significance of these factors is that each is amenable to targeting by various actions or activities to actively and substantially reduce the potential for drugs to accumulate prior to their disposal.

Possible Outcomes from Pollution Prevention: Progress with pollution reduction/prevention activities could yield substantial benefits, including: (i) reductions in the types and quantities of drugs that accumulate, and which then become targets for disposal, (ii) reducing healthcare costs (by lessening wastage from unused drugs), and (iii) improving healthcare outcomes (by ensuring patients are prescribed prudent amounts of medications and that they comply with prescribing directions).

Figure 2



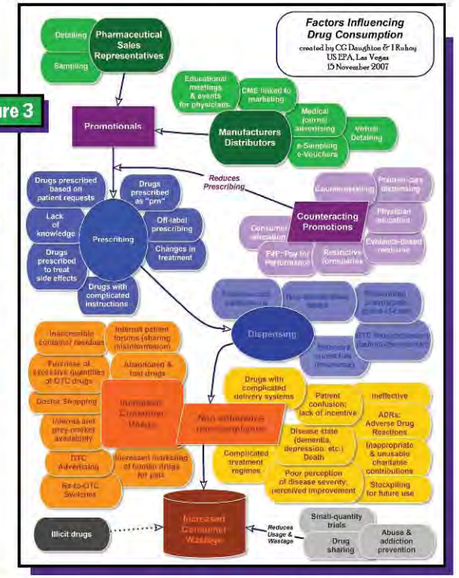
An Objective Approach for Measuring the Magnitude and Significance of Disposal: Finally, a new methodology has been developed for identifying the types, and quantifying the amounts, of individual APIs that are disposed to sewage at the level of the local community. Such a tool had not been previously available. This new approach makes use of the very comprehensive and accurate inventory data collected by coroner offices (Ruhoy and Daughton 2007). Coroners are actually a source of drug disposal themselves as shown in Figures 1 & 2. This approach will lead to an eventual assessment of the relative significance or impact of drug disposal versus excretion/bathing on residues of APIs in the environment.

Conclusions

While the disposal of leftover drugs adds to the environmental burden of drug residues, it is currently not known how significant it might be. By identifying which drugs accumulate (Ruhoy and Daughton 2007), and where they accumulate (Ruhoy and Daughton 2008), measures could be implemented that would not only reduce the consequent need for disposal, but also improve healthcare outcomes and reduce healthcare expenses. This would be done preferably not by focusing on ecologically prudent methods for disposing of leftover medications, but rather by changing the human and healthcare processes that lead to accumulation in the first place — to eliminate accumulation altogether.

If new approaches to medical care were developed that eliminated leftover drugs, the consequent environmental residues would be eliminated, therapeutic outcomes would improve, healthcare expenses would go down, and human morbidity and mortality (due to addictive usage and poisonings from diverted, leftover drugs) would decline. Reducing, minimizing, or eliminating leftover drugs represents a very significant opportunity to improve both ecological and human health.

Figure 3



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available from: http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-1.pdf

PharmEcovigilance & Stewardship: Reducing Human and Ecological Exposure from Pharmaceutical Residues

Christian G. Daughton and Ilene S. Ruhoy

ENVIRONMENTAL ISSUE

Pharmaceuticals can have impacts extending far beyond their intended uses, sometimes with unanticipated consequences for both human health and ecological integrity. The actions and behaviors of those involved in the healthcare system - - from drug manufacturers, physicians, insurers, and pharmacists, to patients themselves - - collectively (and usually unintentionally) contaminate the environment with many of the thousands of active pharmaceutical ingredients (APIs) used in medications. APIs are not always fully destroyed by the body and are then excreted into sewers. APIs applied to the skin have the same fate, as they are washed off during bathing or swimming. Another source for API contaminants is leftover medications, which are often flushed down toilets, tossed into the trash, or stockpiled in the home. Concerns for drug diversion from imprudent disposal in trash or from homes (such as teen recreational use), and accidental poisoning (especially children), have prompted numerous calls (most notably from the White House Office of National Drug Control Policy) for guidance on the prudent disposal of medications.

The work summarized here led to the first conceptualization of a stewardship framework for optimizing the use of pharmaceuticals throughout the healthcare system. Implementing some well-targeted actions in the delivery of health care could have profound, far-reaching benefits for human and ecological health, both of which are intimately linked. By integrating ecological concerns with conventional pharmacovigilance programs that track adverse drug events, a more holistic system for care of both human health and the environment could be created - - one we term *pharmEcovigilance*. Its implementation could reduce the cost of health care, improve therapeutic outcomes, and lessen unintentional acute and chronic exposures of humans and wildlife.

RESEARCH GOAL

The objectives of this project were to:
- Catalog the diversity of locations where drugs are used and accumulate in society - - eventually requiring disposal.
- Define the processes that control and drive the consumption, accumulation, and disposal of human pharmaceuticals.
- Identify opportunities for pollution prevention and source reduction.
- Develop an approach for accurately identifying the APIs (and their actual quantities) being disposed.

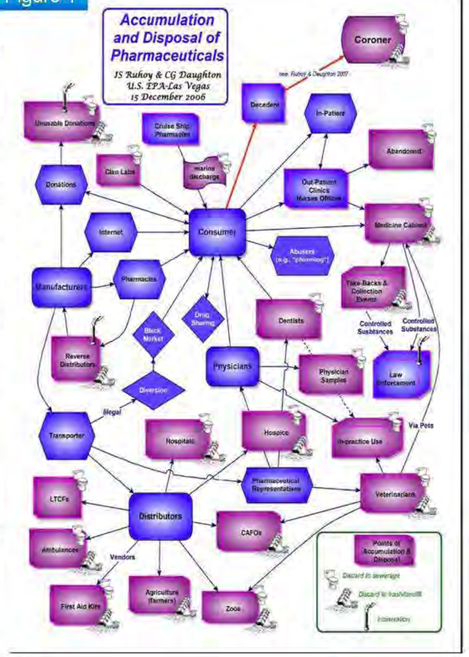
A new methodology was developed for identifying the types, and quantifying the amounts, of individual APIs that are disposed to sewage at the level of the local community. Such a tool had not been previously available. This new approach makes use of the very comprehensive and accurate inventory data collected by coroner offices as shown in Figures 1 & 2. This approach will lead to an eventual assessment of the relative significance or impact of drug disposal versus excretion/bathing on residues of APIs in the environment.

METHODS/RESULTS

Identification of Sources

Probably more than for any other perishable, nonfood item consumed by humans, medications are used and stored at a vast array of locations throughout society. These products are frequently purchased in excess or not fully consumed as directed (e.g., patient non-compliance), leading to the accumulation of unwanted, leftover drugs. A broad spectrum of locations at which drugs are used and can accumulate, eventually leading to disposal, are shown in Figure 1. The relative significance of each of these sources with respect to disposal is currently unknown.

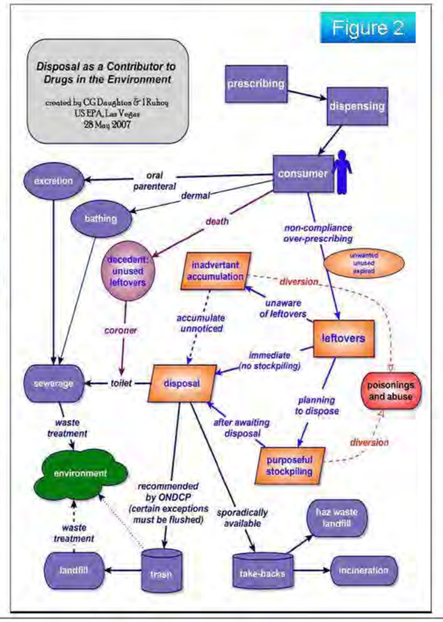
Figure 1



Factors Governing Disposal

The processes leading to the disposal of drugs by the individual consumer are illustrated in Figure 2. A significant point is that accumulated, leftover medications pose several major problems for human health and safety and for the integrity of the environment. These problems result from the diversion of accumulated drugs to those for whom they were not intended (leading to accidental and purposeful poisonings of infants, children, adults, and pets) and from the disposal of accumulated drugs to trash and sewage. The latter promotes the entry of APIs to the ambient environment.

Figure 2



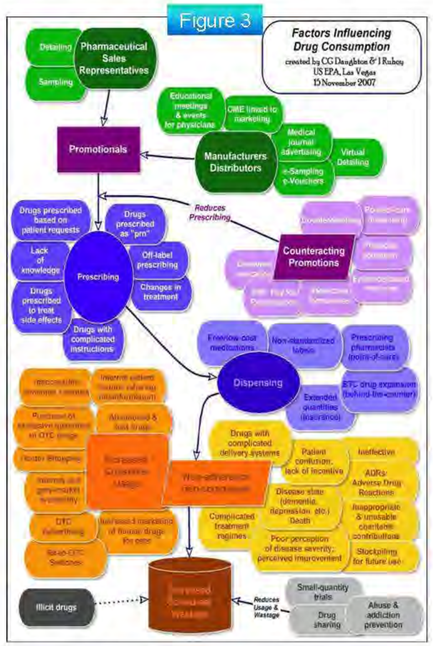
Factors Governing Consumption and Accumulation

Numerous factors affect the consumption of drugs by consumers (Figure 3). Most serve to increase use, although several are at work to reduce use. Most of these factors are amenable to measures that could be designed to reduce their influence on the consumer. The significance of these factors is that each is amenable to targeting by various actions or activities to actively and substantially reduce the potential for drugs to accumulate on-site prior to their disposal.

Possible Outcomes from Pollution Prevention

Pollution reduction/prevention measures aimed at the causes of unwanted, leftover medications could yield substantial benefits, including:
- reductions in the types and quantities of drugs that accumulate, and which then become targets for disposal or diversion,
- reducing healthcare costs (by lessening wastage from unused drugs), and
- improving healthcare outcomes (by ensuring patients are prescribed prudent amounts of medications and that they comply with prescribing directions).

Figure 3



Products & Collaborators

This work resulted in five journal articles, five invited book chapters, a doctoral dissertation, and 12 invited presentations at local, regional, and national conferences [see list of publications at: *Drug Disposal: Ramifications for the Environment and Human Health*, U.S. Environmental Protection Agency, Las Vegas, NV (web page maintained by CG Daughton); available: http://www.epa.gov/ppcp/projects/disposal.html]. Expert consulting was provided to EPA program offices (OSW, OW, and OCHP), Regions, and various stakeholders in the public and private sectors.

CONCLUSIONS

While the disposal of leftover drugs adds to the environmental burden of drug residues, it is currently not known how significant it might be. By identifying which drugs accumulate (Ruhoy and Daughton 2007), and where they accumulate (Ruhoy and Daughton 2008), measures could be implemented that would not only reduce the consequent need for disposal, but also improve healthcare outcomes and reduce healthcare expenses. This would be done preferably not by focusing on ecologically prudent methods for disposing of leftover medications, but rather by changing the human and healthcare processes that lead to accumulation in the first place — to eliminate accumulation altogether.

If new approaches to medical care were developed that eliminated leftover drugs, the consequent environmental residues could be eliminated, therapeutic outcomes could improve, healthcare expenses could go down, and human morbidity and mortality (due to addictive usage 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.

FUTURE DIRECTIONS

A major future focus will be to actively engage the healthcare communities, dispensers, and insurers in a productive dialog and in taking the first steps to address those facets of healthcare contributing to API pollution by adopting a pharmEcovigilance program. *The main focus is on identifying and reducing those sources of APIs that contribute to human and ecological exposure*.

A pharmEcovigilance program would focus on the numerous points along the network spanning from manufacturers to patients - - where medications are designed, packaged, prescribed, dispensed, and consumed, and where numerous processes and procedures could be redesigned to ensure optimal therapeutic outcomes from minimized drug use. The ultimate objective and measure of success would be the degree to which medications are fully consumed (reducing leftovers) while maintaining or improving therapeutic outcomes. Such a program could lead to a more efficient, optimized healthcare system, resulting in a cleaner environment and improved, less-costly treatment outcomes.

Another question needing resolution is determining the overall significance of drug disposal to sewers as a contributing factor for environmental residues of APIs.

IMPACT

This work has been used as a basis for - or to inform or augment decisions regarding - a wide array of actions and activities, some of which include:
- the Committee on Environment and Natural Resources [CENR] Interagency Task Group on Pharmaceuticals in the Environment [PiE],
- Drug Enforcement Administration's policy on drug disposal and the Controlled Substances Act,
- White House Office of National Drug Control Policy's guidance on drug disposal,
- first statewide legislation for the disposal of unwanted drugs (State of Maine),
- EPA's first Drug Disposal Pilot Project grants (OCHP: Office of Children's Health Protection),
- extension of EPA's Universal Waste Rule to pharmaceutical waste,
- OW's Health Services Industry Study for the Effluent Guidelines Program,
- expanding the EPA's PPCPs Literature Database (http://www.epa.gov/ppcp/lit.html),
- the doctoral dissertation for Ilene Ruhoy (MD, PhD) at UNLV,
- several US Senate hearings on PPCPs,
- creation by Touro University of a new Institute of Environmental Medicine,
- responding to numerous inquiries and interviews from regulators, legislators, scientists, public, and press regarding the disposition of unwanted pharmaceuticals.

poster presented at the "Environmental Sciences Division Peer Review," 14 May 2009, National Exposure Research Laboratory, Office of Research and Development, US EPA, Las Vegas, NV, Session 5: Water Quality – Stressor/Receptor Characterization, poster #SRC-3.

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