Examining unused pharmaceuticals in the environment

Ilene Sue Ruhoy
University of Nevada, Las Vegas

Follow this and additional works at: https://digitalscholarship.unlv.edu/rtds

Repository Citation

This Dissertation is brought to you for free and open access by Digital Scholarship@UNLV. It has been accepted for inclusion in UNLV Retrospective Theses & Dissertations by an authorized administrator of Digital Scholarship@UNLV. For more information, please contact digitalscholarship@unlv.edu.
EXAMINING UNUSED PHARMACEUTICALS
IN THE ENVIRONMENT

by

Ilene Sue Ruhoy

Bachelor of Science
Marymount College
1996

Doctorate of Medicine
University of Pittsburgh School of Medicine
2000

A dissertation submitted in partial fulfillment
of the requirements for the

Doctorate of Philosophy Degree in Environmental Studies
Department of Environmental Studies
University of Nevada Las Vegas

Graduate College
University of Nevada, Las Vegas
December 2008
The Dissertation prepared by

Ilene S. Ruhoy

Entitled

Examining Unused Pharmaceuticals in the Environment

is approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Examination Committee Chair

Dean of the Graduate College
ABSTRACT

Examining Unused Pharmaceuticals in the Environment

by

Ilene Sue Ruhoy

Dr. David M. Hassenzahl, Committee Chair
Chair, Department of Environmental Studies
University of Nevada, Las Vegas

Unused pharmaceuticals take an unhealthy toll on both the environment and human health. In the US alone, an estimated $1 billion of prescription drugs are thrown away each year. Increasing availability, marketing, and purchasing of both prescription and over-the-counter medications, coupled with the tendency of patients to discontinue use of and to stockpile drugs at home, is a unique problem that has garnered increasing attention among scientists, policymakers, and the media in the last ten years.

These accumulated household drugs become unused pharmaceutical waste. This waste must be discarded and disposed of by the consumer. Historically, consumers have been instructed by health care professionals to dispose of unwanted medications into the...
sewage system. Inserts in some pharmaceutical packaging have also instructed consumer to flush expired and unused medications down the toilet. This method has historically also applied to pharmaceuticals stored in locations other than the consumer household.

In the past decade studies have consistently identified amounts of pharmaceutical residues in water systems throughout the country. However, it has yet to be determined if the source of these substances found in the waterways is from excretion or disposal. While it is most likely a combination of both, it has been difficult to assess to what extent disposal takes place. Namely, there has been no source of data that would convey how often disposal takes place, what are the more common pharmaceutical compounds disposed, and in what quantities these compounds are flushed into our sewage systems.

This dissertation describes a new methodology – compiling inventory data from coroner offices – which can provide a source of data detailing exactly how much of a specific pharmaceutical ingredient has been disposed in a particular geographic area and the frequency with which that compound is found in the disposal inventories. Further, this work assesses the many, varied, and often overlooked sites of accumulation of unused medications, the approximate relative contributions generated at each site, and common reasons why they accumulate in their respective locations. Finally, this work assesses the risk associated with inappropriate transfers of pharmaceuticals, and potential means for mitigating the risks.
## TABLE OF CONTENTS

| ABSTRACT | iii |
| LIST OF TABLES | vii |
| ACKNOWLEDGMENTS | viii |
| **CHAPTER 1** INTRODUCTION | 1 |
| Environmental and Human Health Impacts | 4 |
| References | 9 |
| **CHAPTER 2** TYPES AND QUANTITIES OF LEFTOVER DRUGS ENTERING THE ENVIRONMENT VIA DISPOSAL TO SEWAGE – REVEALED BY CORONER RECORDS | 12 |
| Overview | 12 |
| Introduction | 13 |
| Background | 23 |
| Methods | 28 |
| Results | 30 |
| Discussion | 35 |
| References | 39 |
| **CHAPTER 2** BEYOND THE MEDICINE CABINET: AN ANALYSIS OF WHERE AND WHY MEDICATIONS ACCUMULATE | 45 |
| Overview | 45 |
| Introduction | 46 |
| Background | 49 |
| Discussion | 55 |
| Conclusions | 81 |
| References | 95 |
| **CHAPTER 4** MANAGING UNUSED PHARMACEUTICALS – A RISK MANAGEMENT PERSPECTIVE | 100 |
| Overview | 100 |
| Introduction | 102 |
| Discussion | 107 |
| Conclusions | 127 |
| References | 128 |
LIST OF TABLES

Table 1  Potential Applications for Coroner Drug Inventories...................................................... 42

Table 2  Summary of API Masses Disposed to Sewerage by a Coroner Office during a 12-month Period ..................................................................................................................... 87

Table 3  Major Opportunities for Preventing the Wastage and Accumulation of Medications ................................................................. 89

Table 4  Unique Aspects of Drug Disposal via Flushing (in contrast with Excretion/Bathing) that could prove Environmentally Significant .................. 91

Table 5  Strategies to Abate the Risk of Transfer of Pharmaceuticals from Households to Inappropriate Locations .................................................. 115
ACKNOWLEDGMENTS

Many individuals have contributed to this dissertation in innumerable ways, and all deserve my considerable thanks. My advisor David Hassenzahl has been a guiding light in my journey into research and academia. David’s advice, encouragement, and humor have been instrumental in my efforts and I thank him for always believing in me.

My mentor Christian Daughton has been tireless and unrelenting in his assistance and friendship. I thank Christian for his personal and intellectual support and for his attention to detail. Christian taught me there is always more to edit.

Thank you to Shawn Gerstenberger who was my first advisor, contact, and professor at UNLV. Shawn forced me to think long and hard about what I wanted and how I was going to get there. Chris Williamson was a sounding board for my various moods and wayward thinking, a consistent attendee at my lectures, and provided many sources of information for my work, without which much of my work would have not been possible. Patricia Markos and Larry Ashley have dedicated their time and commitment to both me and my work and I am thankful for all they have done.

My department and the administration at Touro University of Nevada were patient and understanding at all times. Thank you to Jutta Guadagnoli for her cheerleading and for changing the teaching schedule over and over again to meet my needs. Thank you to Michael Harter, Mitchell Forman, Michael Wells, and Don Havins for caring and offering advice when I sorely needed it. Colleagues such as them are hard to find.
Finally, I thank my family. My husband Steven tolerated my many days away from home with grace and love, my sleepless nights, and my insecure outbursts. He makes all I do worth it and his pride in me is all I can ask for. My daughter Madeline makes my world a better place and inspires me to improve the world at large. Her presence on this earth keeps me grounded and content. I dedicate this work to her.
CHAPTER 1

INTRODUCTION

The occurrence of trace levels of pharmaceuticals in the environment can be the result of intended use, via excretion or bathing, or disposal of the drug via either the toilet or the trash. Every pharmaceutical ingredient has its own pharmacokinetic profile that will dictate how much of the parent drug, or one its metabolites, will be excreted by both the kidney and the bowel. Bathing can result in transfer of some compounds to the environment from use of topically applied medications.

Disposal represents a direct introduction of the parent compound into the environment. This transfer into the environment occurs following the non-use of the drug as it was originally intended, either by prescription or by its storage in a particular site. For example, expired drugs from first-aid kits are routinely flushed and replenished.

Pharmaceuticals go unused for a variety of reasons. Patients may voluntarily discontinue therapy due to expiration, adverse effects, side effects, change in medication regimen, or poor perception of the extent of illness. Studies report 15% of all hospital admissions in 2003 were due to poor compliance or complete cessation of therapy (Gold and McClung, 2006). Poor adherence has been estimated to cost approximately $177 billion annually in health care costs (NCPIE, 2007). A recent survey found that 49% of respondents admitted to forgetting to take their prescribed medication (NCPA, 2006).
This can lead to an inordinate amount of stockpiling of medications in the home – all of which ultimately have to be disposed of.

If the drugs were not to be disposed and instead are allowed to accumulate in their respective locations, the concern is the consequent availability for inappropriate usage of the drugs – either intentionally or unintentionally. There is often a false sense of safety with pharmaceuticals. They are ubiquitous, sold in pharmacies, and prescribed by trusted physicians. Drugs are often left unsecured. The American Association of Poison Control Centers reports that there were approximately 1.5 million pharmaceutical exposures reported to poison control centers in 2004 (Watson, 2005). An exposure, as defined by the AAPCC, refers to an inquiry made to a certified poison center regarding the unintended use or contact with a prescribed medication. Almost 2,500 of these exposures resulted in death. The National Center on Addiction and Substance Abuse reported a 212% increase in the use of controlled drugs by teenagers between 1992 and 2003 (CASA 2003).

The disposal pathway for unused medications is governed by prescription practices and personal behavior. There are two main routes for pharmaceuticals to enter the environment. The first is through normal usage of medicines. After administration, a quantity of the drug, or its metabolites, is excreted from the body. The pharmacokinetic profile of the drug, the dosage consumed, the physiology of the individual, and the efficiency of the wastewater treatment governs release and eventual exposure via this pathway. When a person consumes a medication, depending upon the chemical structure, metabolism, and biochemical interaction of the drug, as well as some genetic variability in physiology, the drug may be either transformed (yielding one or more metabolites)
which are then released from the body, or excreted unaltered with its chemical structure intact.

The second route by which pharmaceuticals can enter the environment, and the focus of this research, is the disposal of out-of-date, unused, or unwanted medicines, which may occur via the sink/toilet or in household garbage that is then taken to landfill sites. Entry into the environment by this route depends on the habits of the patient and the efficiency of prescription practices leading to fewer unfinished prescriptions.

Kuspis and Krenzelok (1996) reported that only 1.4% of Americans surveyed returned unused medication to the pharmacy, whereas 54% threw them in the trash, and 35.4% disposed of them in the sink/toilet. For most people, household garbage is the most straightforward and least time-consuming method of disposal. Even if the return of all pharmaceuticals to a pharmacist or a physician were legal, there is no monetary incentive to return medicines to the pharmacy and it requires more effort than simply discarding them. There would have to be another motivating factor employed to entice the public to participate in a return system of their unused medication.

The question of how to dispose of unwanted and unused pharmaceuticals is proving to be a daunting task. Historically, consumers have been directed by healthcare professionals (i.e., doctors and pharmacists) and poison control centers to flush the medications down the toilet, then pour them down the sink, or throw them into household trash. US Drug Enforcement Administration (DEA) regulations strictly control the transfer of drugs that are controlled substances under the Controlled Substances Act (CSA) (US DOJ, 1970). The CSA was enacted into law by the Congress of the United States as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970.
This law prohibits the transference of any controlled substance from the prescribed individual to any entity other than law enforcement. The consumer is considered the end user and cannot transfer the controlled medication to anyone, including a physician or a pharmacist. This is one of the reasons that most pharmacies will not accept returns from patients.

Abuse of prescription analgesics in 2007 ranks second—only behind marijuana—as the Nation's most prevalent illegal drug problem (ONDCP, 2008). In an effort to combat the rising rates of prescription drug abuse, the White House Office of National Drug Control Policy (ONDCP, 2007) has established the first Federal guidelines for proper disposal of unused drugs. These guidelines, released in February 2007, direct consumers to adulterate unwanted medications by mixing with an unpalatable substance and then disposing into the household trash. Yet the guidelines also include a list of medications with either a perceived or known risk of diversion and toxicity. In order to avoid potential public health consequences, consumers are instructed to flush these medications to ensure they are not available to those who are inclined to sort through public trash or to those who might accidentally ingest them, such as toddlers or pets.

Environmental and Human Health Impacts

The unexamined disposal of unwanted medications has led to concern with regard to the health of the environment beginning in the 1970’s when scientists began to reveal the ability of pharmaceuticals to enter the environment. Garrison et al. (1976) first reported clofibric acid (the active metabolite from the lipid regulators clofibrate, etofibrate, and theofibrate) in raw sewage and activated sludge effluent. Hignite and Azarnoff (1977)
reported the detection of salicylic acid and other drug metabolites in the influent and effluent of a sewage treatment plant in Missouri. A landmark monitoring study published in 2002 by the United States Geological Survey (USGS, 2002) found that 80% of 139 streams sampled across 30 states detected (albeit at low concentrations) chemicals commonly found in prescription drugs.

In waterways from the Potomac to the Brazos River in Texas, researchers have found fish exposed to trace levels of estrogens and antidepressants, and many show evidence of neurological or physiological changes (Folmar et al., 16; Ying, 2008). Several studies have demonstrated detrimental effects on fish species such as alterations in sex ratios, other endocrine disturbances, and abnormal social behaviors (Cleuvers, 2004; Fent et al., 2006).

Advances in analytical chemistry enable us to irrefutably decipher residues of pharmaceuticals in the environment. Detection of chemical compounds at concentrations of parts per billion and parts per trillion are now possible (Hirsch et al. 1999). A recently published study in the Netherlands concluded, based on calculated hazard quotients, the effects of fluoxetine, ibuprofen, and carbamazepine, three very commonly prescribed drugs, place the “environment at risk” (De Lange et al., 2006).

The assessment of detrimental and deleterious effects on the environment includes not only an understanding of the chemical and biological interfaces, but also of the sources from which the chemicals come. Accumulation of pharmaceuticals occurs at many different points in our communities. The sources of pharmaceutical accumulation are the end sites of the drugs – the location they may be found prior to their disposal or perpetual storage. Regardless of the method of disposal, commonly prescribed
medications leave the manufacturer for a fate of either consumption or non-consumption. Non-consumed drugs end up in many sites, including schools and child care facilities, hospitals, nursing homes, hospice care centers, doctor and dentist offices, public use first aid kits, veterinarian offices, farms, military bases, and prisons (Ruhoy and Daughton, 2008).

That pharmaceutical chemicals found in the environment pose a substantial threat to human life is a natural assumption. Data on long-term impacts on human health is limited and varied, but some evidence does seem to point to potential effects. Epidemiological research designed to explore causality of illness has produced increasing evidence that exposure to toxic agents contributes to the escalating burden of human chronic affliction (Hu, 2003; CDC, 2005). Most pharmaceuticals are designed to target specific molecular structures on human cellular receptors. Many receptors are evolutionarily conserved. Their structure and design are ubiquitous among humans as well as across many different species.

A definitive understanding of the relationship between the disposal of pharmaceuticals and environmental impacts still eludes us. The chasms of knowledge with respect to amounts, sources, and interactions stalls the implementation of policy to guide the disposal of drugs that are not used as originally intended. A common controversy is the relative contributions of disposal and human excretion to pharmaceutical residues found in the environment. It is not currently known what portions of the pharmaceutical ingredients found in the environment originate from human disposal.
On a basic level, the extent of disposal of unused medications is poorly documented. An evaluation of human disposal would include rates of prescription and rates and degrees of non-compliance of the most commonly prescribed medications. Non-compliance, referring either to the complete cessation of medication consumption or an alteration to the original treatment plan as directed by a health care practitioner, rates are difficult to assess, however, and the literature often reports varying rates depending upon the disease treated and the treatment used (see Demyttenaere et al., 2008; Horne, 2006; Rains et al., 2006). Even so, an assessment of medication disposal would have to assume a certain percentage of consumers dispose of the drugs while others simply accumulate unused.

While the precise chemical structure of the drugs entering the environment is well known for those instances of disposal, we would still need to further our understanding of its effects on the environment including its retention in our waterways. Currently, our wastewater treatment works are not equipped to remove all pharmaceuticals, or their metabolites. Studies have shown that many pharmaceuticals are not fully removed by sewage treatment systems (Petrovic and Barcelo, 2007). In addition, a comprehensive environmental risk assessment would have to include a spectrum of alternative dose-response relationships, such as the potential synergistic and/or additive effects among the chemicals.

The literature on pharmaceuticals in the environment has exponentially increased during the past decade. The research has mainly focused on the detection and quantification of pharmaceutical compounds found in natural resources as well as some theoretical examination of the correlation between these compounds and the
physiological alterations and aberrations recently seen in aquatic life. There is scant literature on the reasons and amounts of drugs that are disposed and whether this disposal is at all responsible for the concentrations reported in the environment.

This dissertation analyzes the problem of where, how much, and why pharmaceuticals accumulate where they go unused. This issue has garnered attention by many, often competing, interests and factions. One objective is to design a complete assessment of unused pharmaceutical chemicals and the extent and result of their disposal. This contributes to the growing body of knowledge as we begin to understand the extent to which drugs accumulate in our society and then in our natural environment. An ultimate goal would be to foster practices that would lead to reducing the amount of leftover pharmaceuticals, primarily by improving prescription and dispensing behaviors as well as patient compliance. An understanding of the factors governing usage and non-compliance would help to drastically reduce the amount of leftover drugs. To improve patient compliance in the US would not only decrease the quantity of medications to be disposed of, since they would be consumed instead, but would also increase the physician's ability to treat and thereby improve patient outcomes. The continuing surge of prescription rates likely leads to both an increase in use of the drugs and to an increase in non-use.

The pharmaceutical industry continues to develop new molecular entities and, perhaps more importantly, introduces thousands of new formulations and patents on existing chemical entities each year, using isomers of chemical structures already used in clinical medicine. The approval process for new drugs and the post-marketing safety surveillance is fraught with flaws and inadequacies (Michaels, 2008). While these
medications certainly save and improve human lives, the irresponsible and unregulated prescribing of these compounds results in waste. If we are to create a sustainable healthcare system, the environment should be protected from increasing advancements in and continual changes in pharmaceutical chemicals that are not used as intended and subsequently enter the ecosystem, which has not necessarily evolved to withstand the consistent and chronic introduction of toxic foreign compounds. Our environment is resilient but can we expect it to continue to withstand and endure further burden? This will require all those involved in the development, manufacturing, distributing, prescribing, regulating, and utilizing these pharmaceutical chemicals to collaborate to devise a plan to better manage the perception, reception, acceptance, and use of drugs in this country.

This dissertation estimates amounts of releases (Chapter two), the range of accumulation locations in society (Chapter three) and mitigation strategies including pollution prevention (Chapter three) and four-stage risk management (Chapter four). It concludes in Chapter five with a discussion on the impact of this research and recommendations for not only future research but for a renewed approach to greener healthcare.

References


Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest. 2006; 130(1Suppl): 65S-72S.


CHAPTER 2

TYPES AND QUANTITIES OF LEFTOVER DRUGS ENTERING
THE ENVIRONMENT VIA DISPOSAL TO SEWAGE –
REVEALED BY CORONER RECORDS

Overview

Pharmaceuticals designed for humans and animals often remain unused for a variety of reasons, ranging from expiration to a patient’s non-compliance. These leftover, accumulated drugs represent suboptimal delivery of health care and the potential for environmentally unsound disposal, which can pose exposure risks for humans and wildlife. A major unknown with respect to pharmaceuticals as pollutants is what fractions of drug residues occurring in the ambient environment result from discarding leftover drugs. To gauge the significance of leftover pharmaceuticals as potential pollutants, data are needed on the types, quantities, and frequencies with which these drugs accumulate. Absence of these data has prevented assessments of the significance of drug accumulation and disposal as a contributing source of pharmaceutical residues in the environment. One particular source of drug accumulation is those medications that become "orphaned" by the death of a consumer. A new approach to acquiring the data needed to assess the magnitude and extent of drug disposal as a source of environmental pollution is presented by using the inventories of drugs maintained by coroner offices.
The data from one metropolitan coroner’s office demonstrates proof of concept.

Coroner data on leftover drugs are useful for measuring the types and amounts of drugs accumulated by consumers. This inventory also provides an accurate measure of the individual active ingredients actually disposed into sewage by coroners. The types of questions these data can address are presented, and the possible uses of these data for deriving estimates of source contributions from the population at large are discussed. The approach is proposed for nationwide implementation (and automation) to better understand the significance of consumer disposal of medications. Note: This chapter has been previously published as Ruhoy and Daughton 2007.

Introduction

Understanding the scope and magnitude of medication disposal is required for providing: (1) more accurate and comprehensive data for models used for predicting amounts or concentrations of active pharmaceutical ingredients (APIs) introduced to the environment, and (2) a better understanding of the prescribing, dispensing, and consumer consumption practices that lead to the accumulation of leftover (unwanted or unneeded) drugs and which then contribute to human morbidity and mortality via poisonings (Watson et al., 2005). There are two major reasons that leftover drugs are not immediately disposed: (1) inadvertent household accumulation (resulting from drugs languishing unnoticed past their expiry), and (2) purposeful stockpiling (because the consumer is awaiting a satisfactory means for disposal) (see Figure 1).

This chapter introduces a methodology for collecting data to provide evidence-based estimates on the types and quantities of APIs disposed to the environment. While still
rarely used, the records of coroner offices for use in epidemiologic research has been evaluated and recommended by Conroy and Russell (1990). Coroner offices in many locales maintain detailed inventories of medications remaining at sites visited for investigation and acquisition of decedents. Drug stockpiles can serve as a means of obtaining maximum and minimum ranges on the quantities and types of drugs that might have ordinarily been disposed by this subpopulation. These inventories also become an accurate record of the types and quantities of APIs that are actually disposed by coroner offices. This is the first time that an extensive dataset of disposed drugs has been compiled for a well-defined population whose sewage is known to be handled by particular sewage treatment facilities. Such a dataset should permit calculations of average (or minimum) concentrations of APIs introduced via sewage. This is proposed as a general approach that can be widely implemented. The pieces of data, namely, types, dosages, and quantities of remaining pharmaceuticals, collected using this new approach are useful for quantifying or estimating source contributions of pharmaceuticals introduced to the environment and which subsequently could play roles in ecological as well as human exposure, via the natural or artificial recycling of water.

Residues of a wide array of pharmaceuticals are known to occur as contaminants in the environment (Daughton and Ternes, 1999; Halling-Sorensen et al., 1998; Kolpin et al., 2002). A major research gap continues to be an understanding of the relative contributions to these ambient residues resulting from their intended use (such as from excretion and bathing) versus the direct disposal of unwanted, leftover medications. The significance of contributions from direct disposal compared with excretion remains
controversial, largely because there have been no easy means of determining the quantities of medications that are directly disposed, for example to sewage or trash.

The topic of pharmaceuticals as environmental pollutants continues to foster increasing discussion and debate. Various groups, including regulatory agencies, independent organizations, water utilities, and public advocacy groups, have placed high priority on determining whether the existence of APIs in the environment, albeit at low concentrations, pose exposure risks for humans or the environment (Fent et al., 2006). One of the outgrowths of this concern in the US has been increasing interest from local and regional agencies in the implementation of programs designed to take back medications stockpiled by consumers, thereby obviating their disposal directly to the environment. Several states, cities, and counties have successfully implemented both single and recurring collection events for unwanted medications (IISG, 2007). The intention of these "take-back" programs has been to reduce the introduction of APIs to sewerage and trash, from where they can enter the environment as contaminants. The key unknown with these pollution prevention efforts, however, is whether they can significantly reduce the individual or overall loadings of APIs to the environment (Daughton, 2007).

An additional development is the recent federal guidelines for drug disposal. In an effort to combat the rising rates of prescription drug abuse, the White House Office of National Drug Control Policy (ONDCP, 2007) has established, along with the US EPA and the FDA, the first Federal guidelines for proper disposal of unused drugs. These guidelines, released in February 2007, direct consumers to adulterate unwanted medications by mixing with an unpalatable substance and then disposing into the
household trash (except those few whose labels require disposal to sewage because of the acute risk of diversion resulting in human poisonings). While adulterating medications in this manner does not remove the API's potential to enter the natural environment, the intent of these recommendations is to prevent purposeful introduction of medications into sewage while also rendering them unpalatable for those who attempt to reclaim the drugs from the trash for inappropriate use. The federal guidelines also suggest returning leftover drugs to local "take-back" locations, when available. This demonstrates the Federal government's interest in reducing the availability of drugs to those who seek to misuse or abuse prescription medication, while also reducing environmental pollution.

Pharmaceuticals are ubiquitous compounds that have the ability to alter innate human physiological mechanisms. Studies of these compounds as they occur in the environment are unique in various ways. First, these compounds are often detected at such low concentrations (ng L⁻¹) that detection is usually limited to more recent, advanced analytical techniques employed at research laboratories (Daughton, 2007). Second, recent studies (e.g., Heberer, 2002; Radjenovic, 2006; Snyder et al., 2006) have indicated efficient and effective methods (e.g., ozone oxidation) of removing, if not all detectable amounts, a significant percentage of the more commonly studied APIs; note, however, that "removal" can refer to the structural transformation of the API or it can simply refer to the physical relocation or partitioning of the API from the aqueous phase to the solids (sludge) phase. It is important to note that most wastewater treatment plants (WWTPs) in the US do not possess the resources required for the best available treatment technology. Third, controversy remains over whether acute or chronic exposure to pharmaceuticals in our water supply results in detectable human health effects. Finally, and with reference to
the study presented here, while there have been a number of studies that have measured levels of APIs and their metabolites in wastewater, there has been no ready source of data that characterizes the types and masses of APIs disposed via flushing to sewage and whether these amounts are significant with respect to overall environmental loadings (Daughton 2007).

Chemical monitoring studies have provided evidence of the presence of drugs in the aquatic environment (e.g., Fent et al., 2006; Heberer, 2002; Hignite and Azarnoff, 1977; Hirsch et al., 1999), and less frequently in drinking waters, but the sources and their correlations with disposed quantities have proved difficult to determine. There are no datasets that elucidate categories and quantities of drugs that are disposed at any particular time. Coroner offices, however, consistently compile drug disposal data during the ordinary course of investigating and taking custody of the bodies of decedents for each coroner case. A survey of this inventory provides a snapshot and some insights as to the potential extent of unused pharmaceuticals and their disposal. The information gleaned from these under-recognized databases can help guide the identification of drugs to be monitored in the environment and better target where pollution-prevention or source-control efforts should be directed.

Often overlooked are other important possible uses from obtaining comprehensive data on leftover drugs and their disposal. Such data could foster the optimization of prescribing and dispensing practices within the healthcare communities, along with improving communication with patients to improve their adherence to medication regimes. This transformation, by reducing leftover medications, would lessen the consequent need for disposal, and possibly improve healthcare outcomes (Daughton,
2003a). In the ideal world, perfectly functioning prescribing and dispensing systems, coupled with perfect medication adherence by the patient (while noting that one cause of non-adherence is unanticipated adverse effects), would lead to zero drug wastage and completely eliminate the need for disposal of leftovers. Although probably not a realistically achievable goal, any progress in this direction might also improve the quality of healthcare.

The presence of pharmaceuticals in our environment is by no means unexpected. Pharmaceuticals owe their release to the environment to their universal and highly dispersed but cumulative usage by multitudes of individuals (Daughton, 2001). From 1993 to 2003, the number of prescriptions purchased in the US increased 70% (from 2 billion to 3.4 billion) (Kaiser, 2004), while the population increased only 13% (from 257,782,608 to 290,796,023) (US Census Bureau, 2006). The elderly consume an ever-increasing number of medications – some prescribed to counteract the effects and responses of other prescribed medications. At any given time, 40% of those older than 65 years use five or more drugs, and 50% of all adults in the US (greater than 18 years of age) take at least one prescription medicine (Kaufman et al., 2002). In 2005, among the 300 most frequently prescribed pharmaceuticals in the US, more than 2.5 billion prescriptions were written (RxList, 2007). Prescription rates for opioids, benzodiazepines, diuretics, monoamine agonists, anti-infectives, and corticosteroids were the highest among all the medications prescribed.

Unused pharmaceuticals not only pose exposure risks for both the environment and humans, they also reflect lost opportunities for proper therapeutic treatment and wasted healthcare resources. In the US alone, an estimated $1B (US) of prescription drugs are
discarded each year (Strom, 2005) from healthcare institutions such as hospitals, pharmacies, hospices, and long-term care facilities; figures for consumers do not exist. Although procedures are available in the healthcare sector (such as hospitals, pharmacies, hospices and long-term care facilities) for the proper disposal of unused pharmaceuticals, especially for the low percentage that are regulated as hazardous waste, generally these substances are simply disposed to drains (and sometimes to trash) or disposed along with regulated medical waste (Burke and Smith, 2006). These unwanted and unused drugs represent a costly wasted resource for the healthcare system and indicate the growing problem of what to do with unused and unwanted medications or how to minimize their creation. With regard to public health, this wasted resource may reflect inefficiencies in prescribing practices and may indicate sub-optimal delivery of healthcare, impairing or diminishing therapeutic outcomes. Unused, unwanted drugs in consumer homes inadvertently accumulate past expiry or are stockpiled (awaiting disposal) and are therefore available for those (including children) who seek to abuse them or who might ingest them accidentally (Figure 1, end of chapter). Unwanted drugs, moreover, represent a source from where a spectrum of biologically active anthropogenic chemicals can enter the environment. That human health and the health of the environment can be inextricably tied (Daughton, 2003b) is demonstrated perhaps in no better way than the fact that the non-optimum delivery of health care is, in part, a contributing source for pharmaceuticals in the environment, which in turn may play a role in affecting the environment and, therefore, quality of life.

Prior to this approach described for mining coroner data, the only means available for obtaining inventories of drugs destined for disposal was from take-back events or from
physical investigation of municipal trash. Both are highly resource intensive, and as a consequence are of limited informational value. Obtaining data from take-back events requires the efforts of a pharmacist (under the vigilance of law enforcement) to identify and record the identity of the medication, the dosage of the API(s), and the dosage units. These data are already meticulously collected during the course of coroner investigations, requiring no additional work.

Decedent populations could be biased in terms of age and health status. Many decedents are younger and probably represent the norm in terms of health and drug consumption. The drugs inventoried during coroner investigations could therefore possibly be biased in terms of the types of drugs or their formulations, and perhaps biased somewhat high in terms of the quantities on-hand (for those with declining health). In contrast, the drugs returned at local take-back events held on sporadic schedules very possibly represent accumulations over long periods of time (where the consumer had accumulated a backlog of drugs for an entire household while waiting to eventually find out how they could be disposed). This means that the quantities of drugs initially received from a particular individual during a take-back event may be biased high — not representing the amounts that would be returned if take-backs occurred on a continual basis; it is also very difficult to extrapolate to the general population. For the decedent population, the types and quantities of drugs on hand represent the types and amounts that would be found at any point in time for a decedent. For take-backs, however, the quantities of drugs returned cannot easily be used to calculate population accumulation rates because the quantities that any one individual returns could decline over time. Data
would need to be collected over sufficiently long periods of time to obtain representative data.

Coroner investigations do not select for inherently biased populations — namely individuals who were necessarily purposefully saving unwanted drugs. Most decedents had probably been living lives unconnected to any focus on accumulating drugs. In contrast, the population attending take-back events may be biased in terms of those who have purposefully been accumulating leftover drugs while waiting to figure out how to dispose of them.

Another consideration with respect to coroner data is the ability to collect more information regarding the individual, such as age, sex, patient non-compliance, illicit drugs (usually available from police investigation reports), and location of residence. Location is important should it be desired to estimate quantities of APIs that are introduced to sewage within a particular sewage district [in order to calculate concentrations or quantities entering a given Wastewater Treatment Plant (WWTP)]. Compliance is extremely useful to know in order to better design approaches to pollution prevention, such as more vigilant and appropriate prescribing.

Attempts at identifying and quantifying the types and amounts of wasted drugs have often been inadequate in terms of accuracy, consistency, and breadth. Most of the information amassed has been from various one-time local take-back events (CRG 2006). Data collection from these events has never been standardized, and there is no current consensus on the most efficient way to inventory the types and quantities of drugs received over the course of these events. Often reported are just the gross weight and/or volume of the complete, formulated medications, sometimes including the retail
packaging (without note of actual API content), because identifying and measuring the types and amounts of drugs was labor intensive and frequently cost prohibitive. The Unused Medicine Registry (CRG Medical Foundation, 2006) was recently established by the Community of Competence organization in Bellaire, TX to collect information about drugs remaining in the home. The Registry is designed to collect information from community-based drug return programs (take-backs) on the medications received from consumers. While the Registry demonstrates some important trends in unused medication, the data received are from a variety of events, many with different organizational structures and different methodologies used to collect the data. Another major limitation of data collected from take-backs is that the subpopulations of those who return their medications cannot be correlated with the WWTPs that receive their waste, making calculation of API masses introduced to known sewage flows inaccurate or impossible. Other methods of acquiring similar types of data generally focus on waste from institutions such as hospitals and long-term care facilities, which are not necessarily representative of the general population.

The methodology described here allows for the identification and quantification of the APIs actually disposed from a previously unrecognized but common source -- coroner offices. Comprehensive data on medications disposed within one metropolitan county, Clark County, NV, during a calendar year were compiled. The information contained in the greater than 1,600 records includes not only the type of medication found, but the number of pills remaining, the dosage amount of each pill, the date of the prescription, and the prescription directions such as the frequency of the directed consumption. These medications represented greater than 400 different active pharmaceutical ingredients,
encompassing the more commonly prescribed cardiovascular and central nervous system agents to the less often prescribed such as anti-retroviral medications. The complete inventory of medications identified by the Clark County, NV Coroner Office will be published in future publications.

These data provide some insights and measures regarding the contribution to ambient environmental residues of human drugs that result from sewage disposal. If this type of data were to be collected on a nationwide basis, the means for improving the practices for prescribing and dispensing of drugs could eventually lead to minimization of the accumulation of leftover drugs. A major outcome of this new methodology would be an increased understanding of the scope of disposed pharmaceuticals. Such an understanding could lead to new approaches for reducing drug diversion, abuse, and accidental poisonings, as well for improving therapeutic outcomes at lower cost.

Background

It is considered standard protocol by most coroner offices in the US, as described by the National Association of Medical Examiners (NAME, 2007), that when a medical investigator from the coroner’s office arrives upon the scene of a decedent, following the standard procedures regarding the approach to the body and the scene. The investigator will then search for medications, prescribed in the name of the decedent, present on the scene, in case drugs may have contributed to the cause of death. There are some cities, however, where law enforcement services are called to the scene rather than investigators from the coroner’s office; in these cases, the coroner’s office medical investigator plays no role in analyzing or removing anything from the scene and therefore does not have
any role in the disposal of leftover medication – they simply receive the expired body. There currently are no accessible statistics that describe how many cities primarily use law enforcement instead of coroner services, nor is the process of collecting and inventorying medications standardized among them. However, a survey is under preparation to effectively assess the prevalence of coroner offices that operate under these guidelines (Ruhoy, in preparation).

A death becomes a coroner's case when the decedent has either expired alone or the death is considered suspicious by law enforcement. The majority of the coroner cases are due to those deaths that occurred without a witness present. The investigator at the scene records the information found on the medication vial or submits them to Poison Control Services for help in identification. This information includes the prescription number (as labeled by the dispensing pharmacy), the date the prescription was filled, the name of the medication (generic or brand name), the dosage, the directions for taking the medication as prescribed by the physician, the prescribed number of pills (which refers to both tablets and capsules but does not include powders, liquids or alternative drug delivery systems), and the name of the prescribing health care professional. The final and important piece of information recorded by the investigator is the number of pills remaining in the prescription vial. A facsimile of a typical coroners' site-investigation record is shown in Figure 2 (end of chapter).

Following the collection of data on an inventory sheet, the investigator then disposes of the remaining prescription pharmaceuticals. This is done most often via the toilets at the locations of the decedents and always done in the presence of a witness. Occasionally, the medications are disposed of in the garbage of the home, either because of faulty toilet
systems or at the request of family. Disposal is manually recorded along with the signatures of the disposer (usually the investigator) and the witness (usually a family member or a local police officer). These factors all contribute to ensuring a high standard of quality for the collected data.

The medical investigators are “deputized” and, therefore, act as representatives of law enforcement. This is necessary due to US Drug Enforcement Administration (DEA) enforcement of the Controlled Substances Act (CSA) (US DOJ, 1970). The CSA was enacted into law by the Congress of the United States as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. This law prohibits the transference of any controlled substance from the prescribed individual to any entity other than law enforcement (see summary in Daughton, 2007). The consumer is considered the end user and cannot transfer the controlled medication to anyone, including a physician or a pharmacist. All pharmaceuticals identified by the medical examiner are required to be disposed of by the investigator, as opposed to allowing family members to take possession of the leftover drugs. Law enforcement officers are permitted to seize controlled substances. It is permissible, however, for consumers to return unused and unwanted pharmaceuticals to their local police stations.

Medications collected and disposed of by coroner offices are themselves a measurable source of drugs in the environment. Of more interest, however, is the fact that these inventories provide information regarding the categories and dosage amounts of medications that accumulate and require disposal. At the least, if local sewage flow rates are known, coroner disposal data can be used to calculate minimum known introductions to sewage for an individual water treatment plant or watershed; additional sources would
include excretion and bathing, as well as disposal from a wide array of additional sources,
including consumers (Ruhoy and Daughton, 2008). For the purposes of the model
scenarios developed in this discussion, the assumption is that the sole source of an active
pharmaceutical ingredient (API) in sewage would be from direct disposal by coroner
offices. At the maximum, these data could be used to estimate upper boundaries for these
introductions (by assuming similar drug disposal rates across a community’s entire
population, not just from the coroner). The empirically measured load for any given drug
targeted by a monitoring study of sewage influent would fall below or near this imputed
upper bound if excretion were a minor source. An empirically measured concentration for
a drug that is extensively metabolized (i.e., resulting in excretion of minimal parent API)
and that fell near the imputed maximum range would indicate the possibility that disposal
was a significant contributing source.

Knowledge of the categories, types, and quantities of drugs being disposed can help
guide the selection of targets for environmental monitoring and for study of the potential
impacts on both the environment and human health (from inadvertent exposure to
ambient residues from the environment). In this study, the disposed drugs were
introduced to sewage known to be treated by particular, locally serving WWTPs, making
possible the calculations of minimum amounts of APIs introduced to sewage. The data
can also be used, in conjunction with requisite demographics data, to derive virtual
predicted introduction concentrations (PICs) for disposed drugs (concentrations smoothed
over time), for the first time allowing an estimation of the actual or estimated impact of
drug disposal on total environmental loads of pharmaceuticals.
Furthermore, the data may provide valuable insights regarding use, nonuse, and misuse of medications, which can then serve healthcare practitioners in their approach to treatments prescribed. The coroner data also provide some insight to what categories of drugs accumulate due to patient non-compliance, and therefore which drugs have the highest potential for accumulating unused, eventually requiring disposal.

Interpretations that could be derived from the data include patient compliance rates and abuse rates. Patient compliance and adherence is an important issue in the medical community, as it greatly impacts therapeutic outcomes and is a major factor in health care cost (Foxhall, 2007; Haynes, 2006). While these terms are often used interchangeably, non-adherence is when a patient attempts to follow the directions of the physician but is unable to adhere to all instructions for proper use and consumption. Non-compliance, on the other hand, is when a patient, for any number of reasons, willingly chooses to not comply with treatment as prescribed by the healthcare practitioner. There remains a subtle difference and that difference is often disregarded in the literature. This discussion uses the words synonymously since the end-result is very similar.

Compliance is also a major factor leading to the accumulation of drugs in households, and therefore, has direct ramifications for the environment (because of consequent disposal). The rate of compliance is frequently discussed in the medical and pharmacy communities, and wide ranges of rates (ranging essentially from 0% to 100%) are often stated with little supporting data. A report released by the National Community Pharmacists Association and Pharmacists for the Protection of Patient Care states that 38% of consumers questioned had forgotten to take a prescription medication, and 29% of those surveyed said that they had at least once stopped taking a drug before the
prescribed period was over (NCPA, 2006). The same survey found that 74% of respondents admitted to non-compliant behaviors including skipping doses, taking less than the recommended dose, or forgetting to take medication. In a survey by Abahussain et al. (2006), 25.8% of the respondents reported self-discontinuation of treatment regimens. A persisting, unanswered question is the percentage of accumulated, unwanted medications that derives from non-compliant behavior.

Methods

Data as described were collected from the Clark County Coroner's Office (CCCO) in Clark County, Nevada. The total available data were selected from the 13-month period of January 2005 through January 2006 as this was the most recent accessible data for an entire calendar year. In this period, there were 1,632 coroner cases having drugs that were inventoried and therefore suitable to evaluate in this study. The most recent census for Clark County estimates a population of 1.7 million people (US Census Bureau, 2006). Data were then entered into a spreadsheet, reviewed for accuracy by comparing computer records with manual file records, and analyzed.

As indicated on the CCCO website, there were 13,761 deaths reported in Clark County in 2005. Of this total, 10,135 deaths were reported to the Clark County Coroner. The total number of cases accepted as coroner cases was 3,393. Some of these cases, however, were not deaths in the home environment. For example, coroner cases include traffic accidents or bodies found outdoors. For obvious reasons, these case files usually did not include medication inventories. Certain other cases, while located in a home environment, did not have any unused medications to report. Often these cases were
deaths of minors or young adults. The 1,632 cases reviewed (48% of the total coroner cases) represent those cases that contained a medication inventory log. Fifty-eight of the cases reviewed were from January 2006. To consider the data on the basis of a complete calendar year, 1,574 cases therefore contained medication inventory logs during 2005. The cases reviewed represent approximately 11% of all 2005 deaths reported in Clark County. Note that this frequency of occurrence of drug-inventory data may not be representative of the frequency at other locales, but would have no influence on data that might be collected in other locales.

The 2005 death rate for Nevada is comparable with that on a national basis. In 2005, the 13,761 deaths in Clark County’s population of 1.7 million represented a rate of 0.008. In the US, during 2005, there were 2,432,000 deaths in a population of 297.8 million (NCHS, 2006), also a rate of 0.008%. This is significant in terms of relating the populations and extrapolating the data.

The data compiled by the coroner office in Clark County resides in handwritten and/or digital notations recorded by case number. For this study, each case was reviewed for data regarding pharmaceuticals located and disposed of. The listing of the specific pharmaceutical information (such as name of drug, prescription dosage, prescription date, and directions for use) is originally recorded on a written inventory sheet included in each case file; a facsimile example is shown in Figure 2. The information is then entered as a narrative parameter within the coroner database. However, not all cases had been entered into the case database, often due to time constraints of entering multiple medications found in a particular case. Therefore, each case, including its inventory sheet and digital
file, was evaluated manually in order to compile all pharmaceuticals disposed during the research period. Each paper file was reviewed for accuracy and thoroughness.

This information was recorded in an Excel spreadsheet, and masses of APIs disposed of were calculated using the number of doses identified and the dosage strengths reported. The information was alphabetized by API name as well as sorted by pharmaceutical category as listed in the Tarascon Pharmacopoeia (Tarascon, 2007).

It is important to note that sometimes the brand name was listed in the coroner records as opposed to the generic name. For example, furosemide, an oft-prescribed diuretic, was frequently listed as Lasix®. The data were scoured for these inconsistencies, and all brand names were replaced with generic names for proper chemical distinction. In addition, combination drugs, which are developed and prescribed with increasing regularity, were separated into their component APIs. For example, Lortab® was entered into the spreadsheet as both hydrocodone and acetaminophen, with appropriate dose amounts applied.

Results

The 13-month CCCO dataset contained greater than 5,000 discrete entries, representing on average a little over three APIs per decedent. Each entry represented a single API from a medication identified at the scene. A medication is most often identified by the label on the prescription bottle. In some cases, no pills were remaining from a prescription, and the entry then showed zero doses disposed. As described above, those medications that were dispensed as combinations of APIs were separated in the spreadsheet into their components. Therefore, one entry does not necessarily correlate
with just one medication inventoried. Some representative data are presented here for illustrative purposes.

The most prevalent method of disposal for the CCCO was to flush the inventoried medications into the sewage system. Greater than 92% of the medications found at decedent sites were flushed. Approximately 7% of the medications were disposed of in the household trash of the home of the decedent. Less than 1% was incinerated by law enforcement service. This latter disposal route usually occurred when loose, unidentified pills were found. These pills would be collected and transported to the offices of the Coroner and subsequently identified by Las Vegas Poison Control and inventoried. Following this, the Coroner would apply for a court order to dispose of the drugs, since the act of taking them into possession then made these drugs evidence. The court order would allow cremation of the drugs in the possession of the Coroner.

During the 13-month period of this pilot study, at least 325,000 doses of a wide array of drugs were disposed of into the sewage system by the CCCO; in Clark County, this system is serviced by three tertiary treatment plants. This estimate does not include the multitude of other medication formulations (such as powders and liquids) and delivery systems (such as inhalers, patches, and syringes). Powders and liquids were also disposed of into the toilet but were not quantified in this study. Inhalers, patches, and syringes were disposed in the household trash and were not quantified in this study. The 325,000 doses (1 dose = 1 pill/tablet/capsule) represent greater than 102,000,000 milligrams of APIs disposed of into the sewage system over the 13-month period. These 102 kg are specific to the route of toilet disposal. Recognizing the assumption regarding the similarities in death rates between Nevada and the country, it is not unreasonable to
extrapolate these data to obtain an estimate of at least 17.9 billion milligrams (17.9 metric tons) of APIs disposed of annually into the national sewage systems by the deceased population alone (mass disposed by CCCO multiplied by the ratio of the US population to the Clark County population).

The following two examples illustrate the utility of the coroner dataset. First is an API that serves as a contaminant archetype because of its frequency of occurrence in environmental monitoring studies – the anticonvulsant, carbamazepine (CBZ). The second comprises the beta-blocker cardiac medications. Analogous data exist in the dataset for 200 other APIs.

The anticonvulsant CBZ is considered the primary drug for partial and tonic-clonic seizures and is also used in other treatments. While a low percentage (1-3%) of CBZ is excreted unchanged, another portion is excreted as conjugates, which can be hydrolyzed back to the parent CBZ, once released to sewage (Bendz et al., 2005). Therefore, the effluent concentrations often may not be much reduced from influent concentrations. The efficiency of CBZ transformation in WWTPs and in the environment is not high, leading to widespread persistence of measurable ambient, environmental residues (Bendz et al., 2005).

During the 13-month period of the collected data, there were 1,755 tablets of CBZ identified and disposed of in the homes of the decedents. These tablets represented 307,300 milligrams (307 g) of pharmaceutically active CBZ introduced directly into the Clark County sewage system. Since the most common dose prescribed was 200 mg, it would take roughly between 51,000 and 154,000 oral doses of CBZ for excretion to contribute the equivalent of 1,755 tablets of the pharmaceutically active CBZ disposed of
by the CCCO (assuming an excretion rate ranging from 1 to 3%). The Clark County sewage system has average sewage flows of \(144.4 \times 10^6\) gal/day (MGD) (LVWCC, 2007). Assuming a hypothetical, uniform and consistent daily disposal to sewage, a minimum averaged concentration of 1.4 ppt CBZ (see Equation 1) could be expected in the influent, as well as possibly the effluent, from the disposal of CBZ by the CCCO alone.

Equation 1:

\[
(307 \text{ g/13 months}) \times (12 \text{ months/year}) \times (1 \text{ year/365 days}) \times (1 \text{ day/144x10^6 gal}) \times (1 \text{ gal/3.7854 L}) = 0.0014 \times 10^6 \text{ g/L} = 1.4 \text{ ng/L} = 1.4 \text{ ppt CBZ in WWTP influent}
\]

It is important to note that in reality the disposal of medications does not take place at a uniform, constant rate, but rather episodically. This will result in plug-flows that have higher transient concentrations; this is one of the variables involved with fluctuating levels in sewage (Daughton, 2007).

Assuming CCCO serves the entire Las Vegas basin, this population is served by the Clark County Sewage District. The US Census Bureau estimates 1.2 million adults over the age of 18 in Clark County in 2005 (US Census Bureau 2007). However, more specifically, and perhaps more accurately since not only are most prescriptions written for older adults (a result of a greater incidence of polypharmacy), there are approximately 183,000 people in Clark County over the age of 65 (US Census Bureau, 2007). The CCCO data derive from 1,632 cases (over the course of 13 months) and represent approximately 0.0089% of this sub-population. This estimate can be used roughly to correct the estimate of 1.4 ppt (in STP influent) to 157 ppt CBZ disposed by the proportion of the sub-population aged 65 or older in Clark County.

The 1,632 cases represent approximately 307 g of CBZ identified and disposed annually. This is roughly 0.19 g of CBZ per case. As explained above, these deaths
represent 11% of all deaths reported in Clark County in 2005. Assuming similar coroner statistics across all 50 states, 11% of all deaths in the country would be 267,500 yielding a potential 50.8 kg of CBZ being disposed nationwide on an annual basis just by coroner offices.

For the second example, consider the β-adrenergic blockers, commonly referred to as beta-blockers, which are used in the treatment of hypertension, systemic, and ophthalmic disorders. The compiled CCCO data set indicates almost 10,000 leftover beta-blocker pills that were disposed of, translating into almost 900,000 milligrams (900 g) of beta-adrenergic antagonist APIs disposed into sewage.

By using the prescription date listed in the coroner records, dose-frequency instructions, doses remaining, and the date of death, compliance or noncompliance can be ascertained. The data for beta-blockers represented an approximate 33% rate of noncompliance among the decedents for all the medications listed in the inventory. Of great clinical interest, in almost 70% of those noncompliant cases, the cause of death listed by the medical examiner was the precise disease the unused drugs were intended to treat. By contrast, the cause of death listed due to acute toxicity of prescribed drugs, which by definition does not include illicit drugs, was listed in 7% of the cases.

The study decedents possessed an average of seven prescriptions. These medications were the same pharmaceuticals that are commonly prescribed in the general population (RxList, 2007) and were not present in inordinate quantities. While one might expect that those near the end of life would be taking larger quantities of particular pharmaceuticals, for example, opiates for pain, this did not appear in the CCCO data. The number of hydrocodone prescriptions for this data set was 692 (which may be due to high
compliance). This did not necessarily represent one prescription per case since often more than one hydrocodone prescription was listed for a single decedent. While details regarding the number of specific pharmaceutical prescriptions per decedent will be elucidated in future articles, this basic information can be used to assess the comparability of local, state, and national prescribing and dispensing practices. There were an estimated 1.8 million hydrocodone prescriptions in Nevada during 2005 (Haynes, 2005), a state with almost 2.5 million people (US Census Bureau, 2007). In the same year, there were greater than 101 million hydrocodone prescriptions written in the US (RxList, 2007), a country of almost 300 million people (US Census Bureau, 2006). While the ratios of prescriptions to population count in Clark County (42%) and Nevada (72%) are higher than national figures (33%), they most likely represent the upper range, and may be due to local practices and demographics. This information is valuable because it serves to establish the relevance and representativeness of the data with regard to its overall representation of the US population. In addition, it may be easier to address, and alter, prescription and dispensing practices on a local basis. Comparing local prescription behaviors with similar localities and communities may provide information and recommendations for more efficient, effective, and prudent prescription handling.

Discussion

The data collected from the records of coroner offices regarding the quantities and disposal of unused drugs can be used as a comprehensive and accurate data set from which to derive a wealth of information regarding the extent of environmental disposal of pharmaceuticals that span all therapeutic classes; some example applications for these
data are summarized in Table 1. The data can provide insights to answer questions such as, in what quantities are specific medications disposed of, and what categories of medication are commonly found in the coroner offices inventories. The coroner inventory is useful because it includes data on specific drugs with dosage information that were left over following a death, and that are directly disposed into the sewage systems by the coroner staff. The disposed dosage amounts could prove very valuable in better understanding the sources and their relative contributions of drug residues as measured in STP influents or effluents. As additional water monitoring studies are conducted, this information could be helpful in correlating water concentrations and usage patterns among local populations.

The same dataset provides insight into noncompliant behaviors among the population including the abuse and misuse of prescribed medications and prescription trends of the representative geographic area. Combined with the information on disposal, these factors need further evaluation for various scenarios that would have an effect on ambient environmental concentration levels, as well as indicating the efficiency of prescribing and patient education by medical care providers.

Further analysis can reveal those medications that accumulate at rates disproportionate to their dispensed frequencies and those that accumulate at the highest absolute rates and in the highest quantities. Data such as these would be useful, for example, in indicating which drugs experience high non-compliance or are prescribed in excessive quantities. With these data as a guide, it is possible to target these drugs for emphasizing better prescribing (or dispensing) practices, as well as more prudent disposal practices. An additional use for this inventoried data would be to identify those drugs that
have not been the target of monitoring efforts, but yet exist in the coroner data at significantly high rates. For example, greater than 80,000 milligrams of lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, was disposed of. The ACE inhibitors have never been routinely targeted in monitoring studies.

There are two major approaches for ameliorating the disposal issue – source control and pollution prevention. The first would focus on an effective and environmentally friendly way to dispose of pharmaceuticals that go unused. The second reduces the size of the source by reducing the quantities of medications that accumulate and which would have then required disposal. The supply and distribution of medications coupled with the behavior patterns of patients and physicians dictate the amounts of pharmaceuticals having the potential to accumulate. Patient noncompliance to treatment regimes and physician prescription patterns could be addressed to better optimize patient care and reduce accumulations. These approaches may help to limit the accumulation of pharmaceuticals and reduce the ready source of those drugs that are highly addictive and which are abused, misused, or targets of diversion.

Minimizing the need for drug disposal will need to bring together professionals from the health care and insurance industries, government, environmental sciences and policy, and engineering. The research described here, and to be delineated in upcoming publications, begins to address some of the long-standing uncertainties in science that will need to be resolved. It also exposes other areas of a complex web of pharmaceutical sources that are in need of individual disposal strategies, and potential ways in which the amounts of accumulated drugs can be reduced. In addition, the research introduces a source of data that has previously been overlooked – where a potentially large source of
drugs introduced into the environment is already being inventoried and cataloged. This information is valuable for furthering discussions regarding human medication behavior and also provides a basis for future research into determining what quantities of APIs are disposed, and which then serve as a source of APIs that can enter the environment.

A project creating a unified network of inventoried-drug databases from coroner offices around the country could prove highly useful. Such an effort could first compile existing coroner data, and then automate for future collection. These data could be used to improve patient outcomes and reduce costs of health care. In turn, improved prescribing practices should automatically reduce the quantities of medications needing disposal. The purpose of this work is to provide some examples of the types of inferences and deductions that can be derived from coroner data. An overarching objective is to catalyze consideration for adoption of a more comprehensive version of this approach on regional or national scales.

Note Added: Soon after the conclusion of the project reported here, the Clark County Coroner Office began discussions with local hazardous waste transporters regarding the feasibility of removal and transport of their collected leftover decedent drugs to incinerator facilities. The intent is to cease disposal of the pharmaceuticals into sewage. These discussions were partly a result of the information provided by this research project, as well as the desire of local water authorities to comply with the newly issued federal guidelines. The CCCO hopes to develop a model for proper and safe disposal of pharmaceuticals acquired by the coroner.
References


Hignite C and Azarnoff DL. Drugs and drug metabolites as environmental contaminants: chlorophenxyisobutyrate and salicylic acid in sewage water effluent. Life Sci. 1977; 20: 337-342


Coroner drug inventories can be used to:

<table>
<thead>
<tr>
<th>Determine</th>
<th>Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Types and relative amounts of APIs disposed</td>
<td>• Selection of APIs for targeted monitoring in sewage streams and the environment in specific geographic locales</td>
</tr>
<tr>
<td>• Actual quantities of APIs disposed</td>
<td>• Recognition of APIs that are being over-prescribed</td>
</tr>
<tr>
<td>• Fraction of APIs disposed by various routes (e.g., sewage vs. trash)</td>
<td>• Recognition of medications with poor patient compliance</td>
</tr>
<tr>
<td>• Minimum limits on amounts of individual APIs disposed</td>
<td></td>
</tr>
<tr>
<td>• Putative maximum limits on amounts of individual APIs disposed</td>
<td></td>
</tr>
<tr>
<td>• Predicted concentrations introduced to STPs</td>
<td></td>
</tr>
<tr>
<td>• Relative significance of disposal with respect to the overall environmental occurrence of an individual API</td>
<td></td>
</tr>
<tr>
<td>• Those APIs for which disposal is insignificant with respect to their overall environmental occurrence</td>
<td></td>
</tr>
<tr>
<td>• Those APIs for which disposal might play a significant role in their overall environmental occurrence</td>
<td></td>
</tr>
<tr>
<td>• Those medications for which patient compliance rates are low</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Potential Applications for Coroner Drug Inventories
Disposal as a Contributor to Drugs in the Environment

Figure 1: Role of Leftover Drugs in the Exposures of Humans and the Environment
Figure 2: Facsimile of Coroner Inventory Case Record for Medications Remaining from One Decedent. The names of the physicians, Rx numbers, and decedents have been changed.
Overview

Active pharmaceutical ingredients (APIs) from medications can enter the environment as trace contaminants, at individual concentrations generally below a part per billion (μg/L) (Daughton, 2002). APIs enter the environment primarily via the discharge of raw and treated sewage. Residues of unmetabolized APIs from parenteral and enteral drugs are excreted in feces and urine, and topically applied medications are washed from skin during bathing. These trace residues may pose risks for aquatic life and cause concern with regard to subsequent human exposure (Daughton, 2008).

APIs also enter the environment from the disposal of unwanted medications directly to sewers and trash (Bound and Voulvoulis, 2005). The relative significance of this route compared with excretion and bathing is poorly understood and has been subject to much speculation. Two major aspects of uncertainty exist: the percentage of any particular API in the environment originating from disposal is unknown, and disposal undoubtedly occurs from a variety of dispersed 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.

Accumulation of leftover, unwanted drugs poses three major concerns: (i) APIs
disposed to sewage or trash compose a diverse source of potential chemical stressors in
the environment. (ii) Accumulated drugs represent increased potential for drug diversion,
with its attendant risks of unintentional poisonings and abuse. (iii) Leftover drugs
represent wasted healthcare resources and lost opportunities for medical treatment.

The work presented here has four major purposes: (1) Define the processes, actions,
and behaviors that control and drive the consumption, accumulation, and need for
disposal of pharmaceuticals. (2) Provide an overview of the diverse locations where
pharmaceuticals are used and accumulate. (3) Present a summary of the first cataloging of
APIs disposed by a defined subpopulation. (4) Identify opportunities for pollution
prevention and source reduction. Note: This chapter has been previously published as
Ruhoy and Daughton 2008.

Introduction

Pharmaceuticals uses, for both humans and animals, include therapy, disease
prevention, diagnosis, cosmetics, and lifestyle. Residues from hundreds of widely used
active pharmaceutical ingredients (APIs) can gain entry to the environment via a complex
network of sources and pathways, interspersed through numerous parts of society. These
potential contaminants make their way into the environment 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 with respect to the overall concentrations of APIs in the environment. Wildlife and humans can then experience long-term or intermittent exposure to APIs as trace pollutants, primarily via contaminated water and foods.

Of the research accomplished to date regarding sources, fate and transport, exposure, biological effects, waste treatment, and pollution prevention, very little has been directed at the role played by the APIs in the environment originating from disposal of leftover medications compared with APIs introduced into the environment through excretion and bathing. Leftover, unwanted pharmaceuticals (both human and veterinary) tend to accumulate after being set aside, stored, or forgotten — and this occurs at just about any location where people live, work, or visit. Accumulated or stockpiled leftover medications are eventually disposed either through formal collection programs (with disposal generally at hazardous waste landfills or by incineration) or simply by the end-user discarding directly into sewerage or trash. During storage and imprudent disposal (e.g., leaving leftover drugs visible and accessible to others), a leftover drug can be inadvertently diverted to those for whom the medication was never intended. This can lead to poisoning of humans and pets, or can further abuse and addiction. Well-designed, efficient disposal programs hold the potential for preventing unnecessary human (and animal) exposure and poisonings, as well as for reducing environmental pollution.

Many factors cause medications to remain unused, creating leftover drugs that can accumulate. A wide spectrum of forces underlies the generation of leftover drugs, ranging from inefficiencies and certain practices of manufacturers, distributors, prescribers, dispensers, and patients themselves. Although design of environmentally prudent and safe disposal programs is currently being pursued (Reid, 2007), much of the need for
drug disposal could be eliminated by focusing corrective actions on these major causes of accumulation with the design and implementation of pollution prevention measures. Such practices would be part of a larger program that oversees all the aspects of unintended, adverse consequences of medications. Such a program has been termed pharmEcovigilance (Daughton and Ruhoy, 2008).

Leftover medications pose an acute exposure hazard for both humans and the environment. Opportunities are lost for optimal delivery of healthcare, and valuable healthcare resources are squandered. The likelihood also greatly increases for drug diversion and environmentally unsound disposal. These latter two liabilities can pose acute and chronic poisoning risks for humans and wildlife alike (Daughton, 2007).

This research focuses on two major aspects of the larger topic of pharmaceuticals as environmental pollutants: (i) the processes, actions, activities, events, and behaviors that cause drug wastage (leading to accumulation and disposal), and (ii) the many and diverse physical sources from which stored and accumulated drugs can enter the environment as a result of disposal. Such information should prove useful for the design of pollution prevention measures that encompass a significant portion of the life cycle of medications. Presented here is the first comprehensive examination of the reasons that medications accumulate and the many potential sources or locations from where leftover drugs are disposed. Better understanding of the many and varied origins and sources of leftover drugs will allow for the design of pollution prevention actions best tailored to minimize or eliminate these accumulations, and therefore eliminate or reduce the need for disposal.
Background

The use of human and veterinary pharmaceuticals for their intended purposes is accompanied by a very complex network of routes by which APIs eventually gain entry to the environment or result in unintended direct exposures to humans and wildlife (see Daughton, 2008, Figure 1; 2007, Figure 1). A holistic, integrated view of the life-cycle of pharmaceuticals includes not just the intended uses of drugs, but also their unintended consequences. A broad spectrum of unanswered questions surrounds the environmental lifecycles of drugs (Daughton, 2004). The accumulation and disposal of leftover drugs is but one of their routes to the environment. In contrast to excretion, however, this route of release is more amenable to moderation by environmental stewardship programs, especially those designed around pollution prevention (Daughton, 2002, 2003a, b). To design and gauge the success of such pollution prevention programs, the origins and sources of drug release need to be defined, and the absolute or relative contributions of these sources to the overall loadings of APIs in the environment need to be known. The individual percentages probably vary dramatically among APIs and among the types of packaging (for example, unit-packaged pills are probably not frequently disposed via toilets, whereas liquids are probably routinely poured down drains). In particular, disposal could prove to be a significant source for those APIs that would otherwise have been extensively metabolized.

Of the major sources and routes by which drugs gain entry to the environment, the types and quantities of APIs introduced to sewage as an unintentional result of their intended use (primarily as a result of excretion and bathing) are amenable to estimation using modeling based on usage data combined with parameters such as pharmacokinetics
(portion of parent API excreted unchanged) and known efficiencies of removal from sewage treatment; such an approach has been used by Kostich and Lazorchak (2007). In contrast, gaining an understanding of the types and quantities of APIs introduced directly and purposefully to the environment by the disposal of unwanted, leftover drugs has been more problematic because of a dearth of comprehensive or reliable data. Of the total loadings of a particular API in the environment, it is unknown what fraction results from drug disposal. Chapter 2 presented a novel methodology for obtaining comprehensive and accurate drug disposal data at the community level by the use of existing drug inventories collected during coroner investigations. These unique data can then be used for a variety of purposes (see also Ruhoy and Daughton, 2007).

Another important aspect of drug disposal, and one that is elucidated further in this chapter, is the location at which leftover, unwanted medications accumulate. Probably more than for any other perishable, non-food item consumed by humans, medications are used and stored at a vast array of locations throughout society, including schools and nurseries, hospitals, nursing homes, hospice care centers, emergency shelters, humanitarian organization locations, doctor and dentist offices, public-use first aid kits, veterinarian offices, farms, military bases, and prisons, among others. These products are frequently prescribed, dispensed, or purchased in excess or are not fully consumed as directed (e.g., as a result of poor compliance among patients), leading to the accumulation of unwanted, leftover drugs. A variety of other factors also promote drug wastage; bulk packaging of certain OTC drugs in quantities that cannot be consumed before expiry is one example. These factors have been categorized by Daughton and Ruhoy (2008).
Unused pharmaceuticals pose unknown risks for the environment and take a toll on human health. Based on data obtained in 1999 from a series of retirement communities, Morgan (2001) roughly estimated that the annual value of wasted medications just for adults older than 65 years in the US could exceed $1B; this represented 2.3% of total medication costs. The accumulation of non-utilized pharmaceuticals designed to treat human maladies as well as to treat and care for both domestic and farm-reared animals is emblematic of a society-wide problem that affects both human and ecological health. It is also one whose prevention could lead to immediate benefits for both.

The existence and extent of unused pharmaceuticals could be adopted as a direct measure of non-compliance and poor adherence by the patient population. Non-compliance is often a significant factor in reducing the physician’s ability to treat and can lead to poor therapeutic outcomes. The collective volumes of excess and unused medication can lead to unintentional pharmaceutical poisonings of children (resulting in morbidity and mortality), facilitate abusive use, and promote emerging social problems such as teenage "pharming" (the theft and communal sharing and abuse of pharmaceuticals by teenagers) (SAMHSA, 2007). In addition, the subsequent imprudent disposal of unwanted drugs via domestic trash (e.g., in unsecured containers) encourages and facilitates their reclamation by others (especially addicts) for non-medical purposes.

A better understanding of medication usage could lead to the design of processes that could reduce or eliminate the very need for drug disposal. Two aspects must be considered: (1) the factors that lead to the generation of leftover, unwanted medications, causing them to accumulate unused, eventually becoming wastes, and (2) the many and varied locations and sites in society where medications accumulate (the relative
significance of each source of accumulation is currently not known). The first step is to catalog the sources and assess why drugs accumulate at these locations.

A major question is whether implementing any number of pollution prevention or stewardship measures could control the disposal of drugs. What causes or drives the need for disposal, and can the incidence or magnitude of disposal be better understood and reduced or eliminated?

Note that the current approach to preventing pollution from drug disposal is to implement various means for collecting leftover drugs and disposing of them in the most prudent manner available (primarily as hazardous waste) (Glassmeyer et al., 2008). For those countries (e.g., Australia, Canada, France, New Zealand, Sweden, UK) having formal collection programs for unwanted drugs (those no longer in the commercial distribution/sales system), the most common approach is for consumers to return their medications to local pharmacies; for collection practices in the US, see discussion of Glassmeyer et al (2008) and examples cited by IISG (2007). These “down-stream” approaches are generically termed consumer "take-back" or "return" programs. In the US, the design of take-back programs is much more complicated, as medications cannot be returned to operational pharmacies (unless a formal FDA recall has been issued); several federal regulations currently make any type of universal collection program extremely complex and inefficient (see background presented in Daughton, 2007). This, coupled with the growing imperative in the US to prevent drug diversion, prompted the White House Office of National Drug Control Policy (ONDCP, in conference with the FDA and EPA) to implement guidance for consumers for disposing of drugs in a manner that
reduces entry of APIs to the environment while also protecting public (and animal) health by minimizing diversion and accidental exposure (Daughton, 2007).

Regardless of whether efficient collection programs can be developed for public use, none will ever capture all medications that accumulate as wastes; no type of disposal process (whether landfillsing as hazardous waste, incineration, or other type of complete destruction) is free of the potential to generate hazardous by-products or release pollutants in the future; and all have energy costs for transportation, storage, or destruction. Instead, the optimal approach could be to prevent the need for disposal in the first place — an “up-stream” approach that maximally protects the environment and at the same time has the potential to improve health-care outcomes, reduce healthcare costs, and lessen the incidence of morbidity and mortality caused by human (and animal) exposure to unsecured, unwanted drugs.

Numerous factors play roles in the accumulation of drugs by end-users, whether they are healthcare professionals, physicians, patients themselves, veterinarians, farmers, or humanitarian relief workers. Some of these factors are expiry, patient non-compliance, and over-prescribing or excessive purchase; these have been summarized by Daughton and Ruhoy (2008). Patients will discontinue taking medication due to, among other reasons, intolerable or adverse effects, inconvenience in dosing schedule, a change in therapy as prescribed by their physician, forgetfulness, or even a poor perception of the severity of their illness. Expiration is an oft-cited reason for accumulated drugs; however, other numerous factors play a significant role (Pound et al., 2005). Poor adherence and non-compliance continues to be a major source of public health concern (DHHS, 1990). Significantly, the numbers of consumers who do not follow medication regimens in the
US continue to be substantial, and addressing the causes could improve outcomes and reduce morbidity and mortality (Bosworth et al., 2006; O’Donohue and Levensky, 2006).

Sites of drug accumulation extend far beyond the household medicine cabinet. Some drugs are simply forgotten by consumers at a distant location (i.e., hotels, workplace, and hospitals) and some are intentionally abandoned. Physician and dentist offices have supplies of drugs on hand for intra-office procedures and sample dispensation. However, some areas of substantial drug wastage are independent of the individual consumer as a patient. These locations are associated with the demands and expectations of the public for the easy accessibility and availability of medications. Public buildings, vacation areas and marine vessels, and societal institutions such as prison systems and military bases are all locations where drugs are stored in significant quantities in case the need arises. This prophylactic approach increases the probability of eventual expiration or simply non-use of the medications, thus necessitating their disposal.

The effort to address unused pharmaceuticals must examine all aspects of licit drug use and non-use. While consumer non-compliance is a significant factor, a strategy to combat pharmaceutical waste should include preventative measures that encompass all facets of drug accumulation and waste.

An overview of the diverse spectrum of locations where drug buildup and eventual disposal could occur is presented in Figure 3. It begins with the actual production of the pharmaceutical and traces the many places a drug may end up in following its purchase, whether by prescription, over-the-counter, or by other means such as the gray market. Each rectangular box shown in three dimensions in the flow chart represents a particular site where accumulated human and animal medications might be found.
For each location represented, discussion is presented on where drugs can reside, possible causes for their accumulation at each particular site (e.g., expiry, over-prescribing, etc.), the method by which they accumulate (e.g., abandoned, orphaned, stockpiled), and the problems posed by their accumulation (e.g., diversion, disposal, etc.).

Leftover drugs can indicate medical therapy was never completed, the medication was the incorrect choice of treatment, or that healthcare resources have been wasted. The accumulation of these leftover drugs can further lead to or promote diversion to others, resulting in drug abuse or purposeful human poisonings, or accidental poisonings in humans (especially children and the elderly) or pets because of unsecured stockpiling. Eventual disposal of the accumulated drugs may maximize the introduction of APIs to the environment by circumventing natural physiological processes that ordinarily might have reduced their amounts via excretion. Disposal may also result in acute wildlife poisonings (Daughton, 2007).

Discussion

The origin of all pharmaceuticals is probably the simplest part of the puzzle. Pharmaceuticals are manufactured and produced within facilities owned or contracted by the individual pharmaceutical company. Following their manufacture and production, the drugs are transported to those entities that are then charged with distribution of the drugs. These entities include both traditional brick-and-mortar pharmacies and online e-commerce pharmacies (some of which operate illegally as “rogue” pharmacies), and distribution companies (often a subsidiary of the pharmaceutical company itself);
distribution companies stock other locations that may manage their own internal pharmacies, which may themselves become points of accumulation.

Currently, database and inventory technology allows for very efficient manufacture and distribution. Manufacturing companies are able to accurately estimate demand and potential orders from their various customer retailers and wholesalers (Smith, 2007). This allows them to produce exactly what is needed, when it is needed, and therefore produce very little, if any, unused and unwanted medications that can accumulate. For a discussion on waste generation during the medication production process itself, which is not a topic of this discussion, see Velagaleti and Burns (2007).

The following discussion describes and evaluates: (1) the factors that lead to the generation of leftover, unwanted medications and (2) the many and varied locations and sites in society where medications accumulate and from where they are subject to disposal.

Actions designed to control the many factors that lead to drug wastage and accumulation clearly could help in reducing the types and quantities of APIs that are eventually introduced to the environment by way of disposal. Note that while these factors can also play roles in increasing the unintended release of APIs to the environment via excretion (improving patient compliance is one example), a wide spectrum of other factors contribute more to the over-usage of drugs, resulting in the unnecessarily higher excretion rates of APIs. Many of these factors have been summarized by Daughton (2003 a, b); two examples include the manufacture of racemic drugs (where only one optical isomer is the therapeutic entity) and the use of unnecessarily high doses and durations of treatment (which often are established
expressly for clinical trials in order to maximize the chances of favorable outcomes but
which are never reevaluated or adjusted downward once the drug reaches final approval).
In fact, downward-adjustment of doses by the patient (self-regulation) is a major factor in
"non-compliance," and is caused by patients’ concerns regarding the medications
themselves (Pound et al., 2005).

Figure 4 demonstrates the many factors that influence drug usage - - and therefore
pharmaceutical wastage and accumulation. Identifying and assessing these parameters is
an important first step in recognizing the points where pollution prevention efforts could
be designed and implemented.

Factors Leading to the Generation of Leftover, Unwanted Medication

Promotionals

York University (2008) researchers estimate the US pharmaceutical industry spends
almost twice as much on promotion as it does on research and development. Promotional
items and programs put forth by both pharmaceutical sales representatives ("sales reps")
and manufacturers and distributors target both the general population or specific sub-
populations and carry a positive message with regard to the use and benefits of
consuming prescribed pharmaceuticals. Manufacturers, distributors, and sales reps use
various approaches for promotionals to induce, entice, or convince physicians and other
healthcare professionals of the effectiveness and the appropriateness of prescribing their
drug to a particular patient population. These promotionals can be in the form of
advertising in medical journals, continuing medical education (CME) credits in exchange
for participation in a marketing program, and hosting various conferences, meetings, and
workshops. Furthermore, an aggressive campaign of "sampling" (providing sample packages of the medication at no cost to the physician) and "detailing" new, as well as older, products can influence the extent to which a healthcare professional will consider a drug product in treating a particular patient and/or disease.

Consumers and physicians both report that prescription drug advertisements are increasingly influential. Surveys of patients and physicians have concluded that patients have asked their doctor about a medication solely as a result of direct-to-consumer (DTC) marketing, and physicians then consider prescribing such medications as a result of the patient’s request (Rosenthal, 2003). It is probable that DTC advertising brings more patients into a doctor’s office seeking a prescription for a particular drug (Donohue and Berndt, 2004).

Concerns regarding conflicts of interest --- for example, a particular manufacturer hosting a CME course (which physicians and other professional are required to obtain on a yearly basis in order for their practicing license to remain in effect) --- have been discussed by various law and health groups but no consensus course of action has been reached. If these promotionals were limited and regulated, there would be much less direct interaction and correspondence between those that produce and sell the drug and those who can alter its rate of prescription and, hence, consumption. Indeed, the recently reauthorized Prescription Drug User Fee Act (PDUFA) provides greater authorization and resources for the FDA to evaluate and assess the safety of new medications as well as public advertising (US FDA, 2007). Furthermore, several academic medical centers across the country are instituting policies of their own with regard to the relationships between doctors and relevant industries. For example, the University of Pittsburgh...
School Of Medicine has established a program that provides for the prohibition of gifts and free lunches, addresses faculty speaking and consulting involvements, and disallows the presence of pharmaceutical representatives from patient areas (http://www.coi.pitt.edu/IndustryRelationships/index.htm) (also see: Tregaskis, 2008).

Counteracting Promotions

Counter-promotion involves programs and interventions to teach health professionals or students to critically assess drug promotion, i.e., to teach health professionals how to interact with sales representatives and interpret promotional information. Norris et al. (2005) describes programs that are intended to question the claims made by drug manufacturers in advertisements and educational materials directed at both patients and physicians. The effect of these counter-promotional activities is still unknown for they are still far outnumbered by the promotional programs. In the US, the American Medical Association has guidelines about gifts from the pharmaceutical industry incorporated in its Code of Ethics (http://www.ama-assn.org/ama/pub/category/5689.html). These suggest that gifts to doctors should primarily benefit patients and should not be of substantial value. Further guidelines for regulating interactions between healthcare practitioners and student doctors are needed to establish positive and beneficial relationship with regard to the proper use and prescribing of medications.

Prescribing

Prescribing medications to treat disease is not a simple and straightforward procedure. There are many factors and considerations, not all of which are justified by the literature (especially by evidence obtained from double-blind randomized controlled trials), that influence decisions to prescribe and what to prescribe.
As already discussed, DTC advertising has a direct effect on the knowledge base, and therefore the perspective and desires, of a patient. A doctor may be persuaded to consider a specific medication in the face of an ardent patient. In addition, if a physician were to disagree with a patient’s request and prescribe an alternative medication, this may affect the adherence of the patient to the medication, as well as adversely affect the relationship between physician and patient (Pound et al., 2005; van Dulmen et al., 2008).

Direct-to-physician marketing may play a role as well. Pharmaceutical manufacturers not only advertise to physicians via conventional methods (i.e., medical journals), but also dispatch representatives of the company to regularly visit and educate physicians, physicians-in-training, and office staff on their products – both old and new. These visits (referred to as “detailing”) often include boxes of free samples (referred to as “sampling”) of the pharmaceutical product as well as meals and marketing trinkets such as pens, clipboards, and cups. Human nature as it is, it is easy to believe this communication style may play a role in the physicians awareness and knowledge of medications to be used to treat a particular ailment. Manchanda et al. (2005) outlined the various research on physician and patient learning about drugs.

Optimal prescribing behaviors are complicated and time-consuming. While much of medicine is practiced using algorithms and protocols, often there is not one perfect method of treating a chronic ailment, and each patient needs to be regularly monitored and managed. Genetic medicine (sometimes called “efficacy pharmacogenetics”) is teaching us that each individual may have a different response to treatment as well as a different course of disease. Drugs can have many polymorphic mechanisms and result in various physiological effects and changes in different individuals (Foxhall, 2008). Yet
treatment is often arrived at based on the conventional generic methods of treatment of a disease as well as experience of the physician with beneficial responses in other patients. Regardless, without careful adherence to evidence-based medicine coupled with individualized therapy and treatment, there is the potential for increased misuse, mismanagement, and non-compliance with the medication.

Dispensing

Dispensing practices can affect medication usage. Dispensing refers to the method and form by which a prescription is filled for a patient. Many pharmaceuticals are offered in multiple forms – pill (which may be swallowable, chewable, or sublingual), liquid, intramuscular injection, spray (which may also be used intraorally or intranasally), creams or gels (dermally or intravaginally), suppositories (intravaginal or intraanal), delivery devices (e.g., patches, intravaginal rings), aerosols (inhalement), or drops (eye or ear); each of these can pose different challenges with regard to disposal; used delivery devices, in particular, can contain large amounts of unchanged API. The form of drug delivery can greatly affect a patient’s perception, willingness, and comfort in consuming the medication. In addition, these forms can be prescribed and dispensed in different quantities and using different methods. For example, chronically used drugs can be prescribed in quantities sufficient for one course (with approved refills) or multiple months (normally 90-day supply). Indeed, many pharmacy chains have promotions that encourage increased purchase of certain medications by offering lower prices for a 90-day supply or by offering additional OTC medications at drastically reduced prices. While certainly this is a convenience to the consumer who will theoretically not have to travel to the pharmacy as often to retrieve prescribed medications, the larger supply
stored in their homes increases the quantity of unused medication in the case of altered
treatment by their doctor or in the event of their death. Indeed, some mail-order programs
send automatic refills of 90-day supplies, leading to a continuing accumulation of unused
medications upon a patient's death.

Some medications are dispensed using methods that are intended to improve
medication usage. For example, birth control pills, usually some combination of
estrogens and progestagens, are dispensed in unit-dose packaging. This serves to assist
the user in adhering to the once-a-day regimen. Unit-dose dispensing was originally
designed for hospitals to help reduce medication dispensing errors. However, there are
some medications that are prescribed in the out-patient setting in unit-dose packaging.
The commonly prescribed "Z-Pak" (azithromycin) is prescribed in a pack of individually
wrapped tablets – each corresponding to a day of the week, which is the extent of the
course of treatment. Methylprednisone, a steroid used to treat chronic inflammatory
diseases, can be prescribed in unit-of-use packaging (Lipowski et al 2002) to encourage
proper weaning of the patient from steroid use and avoid the complications of incorrect,
abrupt discontinuation. Technology for pharmacy repackaging of bulk drugs in unit-dose,
unit-of-use, or multi-dose strips, together with day and time reminders (calendar labeling)
are now available (as one example, see Parata Systems:

Finally, dispensing of medication may sometimes be a confusing task in light of the
many drugs that have similar sounding (and similar spelled) names. Barbella (2008)
reports that greater than 1,400 commonly prescribed drugs are implicated in drug errors
due to similar looking drugs or similar sounding names. This is often attributed to poor
phone communication, poor facsimile quality, and poor penmanship on the part of the physician. Dispensing incorrect drugs can lead to pharmaceutical accumulation from cessation of therapy due to poor response or the awareness of the error. Much of this confusion could be eliminated with widespread adoption of electronic prescribing ("e-prescribing").

Non-Adherence and Non-Compliance

Non-adherence and non-compliance to prescribed treatment regimens is a significant and widespread public health issue. Poor compliance and adherence continues to thwart and retard efforts by healthcare practitioners to effectively and efficiently treat symptoms and progression of a wide spectrum of diseases (NCPIE, 2007).

Research on compliance indicates a wide range of non-compliance rates. Reported non-compliance rates are specific for the disease being treated and the treatment itself. For example, there is a higher incidence of non-compliance for clinical depression and for drugs that are prescribed for long-term treatment of a chronic disorder. The World Health Organization’s (WHO) 2003 report on adherence to long-term therapies states that 50% of patients treated for chronic diseases in the US do not take their medication properly (and a portion of this is from failure to complete a course of treatment), 30% of all refillable prescriptions are never filled, and 17-20% of all new prescriptions are never filled. While failure to fill or refill a prescription does not add to the accumulation of leftover drugs, it is possibly an indirect indicator of failure to complete the prior prescription or failure to fully consume free samples; it might also, however, simply reflect a physician’s recent change in treatment, which was the most frequent cause of returned drugs reported by Langley et al. (2005).
Certainly the important factors associated with non-compliance that have been identified are the severity of the condition, salience of the condition, and cost and misconceptions regarding the therapy. Additional reasons why patients intentionally and unintentionally cease treatment are varied as well. They include drugs with difficult or awkward delivery systems (i.e., intramuscular or subcutaneous injections), adverse and side effects, numerous psychosocial factors (e.g., fear of reliance or addiction), and even sensory aversion. Worthington (2007) discusses the positive effect on compliance from a drug’s aesthetics, such as its taste, smell, appearance and touch. Pound et al. (2005) provide a thorough synthesis of much of the extensive literature on why patients resist, avoid, ignore, forget, or alter directions for prescribed medications. The reasons are countless and highly complex – as evidenced by the fact that non-compliance persists in being an extremely perplexing and refractory problem faced by medicine. 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.”

Patients may decide they do not really need the medication due to misjudgment of their health status. This is a difficult obstacle, as many factors can lead to confusion. Misjudgment of health status and the need for a medication can also result from diseases that do not exhibit obvious signs or symptoms; this can be a disincentive for continued treatment. There also may be a breakdown in communication between the prescriber and the patient. While physicians may believe they have explained disease and relevant physiology of disease and drug mode of action, in reality, patient may not understand and become fearful, intimidated, or too anxious to ask the appropriate questions. Another
reason for poor perception is the overall patient-doctor relationship. Adherence partly
depends on the prescriber’s ability to communicate the need and utility of the intended
treatment. This is turn would depend on the patient’s perception of the physician’s
concern, sincerity, and competence.

Locations and Sites in Society Where Medications Accumulate

First-Aid Kits

First-aid kits are probably present in nearly every public building. The Occupational
Safety and Health Administration (OSHA) require first aid kits to be readily available to
the public. Therefore, depending upon the size of the location and the estimated public
traffic, there may be multiple kits present in the building at any given time. First-aid kits
are no longer simply bandages, ankle supports, and some gauze. Today, any consumer or
business organization can purchase first-aid kits that contain anti-diarrheal medications,
antiemetics, antihistamines, analgesics and antipyretics (e.g., NSAIDs, ibuprofen,
aspirin), antiseptics and biocides (which include antibiotics), cold tablets, cough syrups
and drops, antacids, as well as medication for motion sickness, menstrual cramps, and
stomach upsets. First aid kits are also ubiquitous at a wide spectrum of other venues, such
as athletic facilities, camps, all forms of transportation (cars, trucks, trains, boats,
airplanes, etc.), and travelers’ suitcases.

First-aid kits can be specific to the type of institution in which they reside. For
example, Henry et al. (2006) recommends a school first-aid kit for asthma. Given the
increasing incidence of asthma diagnoses in children, it is most certainly prudent for
educators to be familiar with the disease, its signs, and its management. The recommended
“asthma first-aid kit” includes a bronchodilator agent. Since first-aid kits are usually used sporadically, their contents often reach expiry. Furthermore, kits often must be stored in locations that experience high temperatures and therefore their contents can reach expiry very fast. Kits supplied by companies are routinely purged of expired contents, while others are replenished on an ad-lib basis. Regardless, the expired drugs are disposed by kit-provider personnel usually via the sewerage (personal communications).

Physician Samples

Dispensing and use practices contribute directly to the generation of leftover, unwanted pharmaceuticals and may therefore provide opportunities for reducing the quantity of waste. One practice that is often overlooked, and often considered only beneficial to the patient population, is the use of physician samples. Samples, often called “starter packs,” are specifically packaged samples of drugs provided free by pharmaceutical representatives to doctors (a practice termed “sampling”), often as part of a marketing strategy or as a means of gaining access to the doctor. The intention is to provide patients with a “starter” supply that will serve to treat in the interim of receiving the prescription at the physician’s office and until the prescription is filled at the pharmacy. It is also considered a cost-saving measure since a sample sometimes provides the entire course of a short-term treatment or the course of a testing period to assess how the patient will respond to the drug before a full prescription is given (thereby avoiding the prescribing of larger quantities that might otherwise never be fully consumed).

Firm figures regarding the dollar value of promotions in the US are not available. In 1999, drug companies gave doctors free medications worth more than $7.2B at retail (nearly 10% more than the year before) (Petersen, 2000). The most current analysis,
however, indicates that promotions in 2004 alone may have a market value ranging up to $57.5B, or roughly $61,000 per physician in the US. Samples alone may represent about $15B (Gagnon and Lexchin, 2007).

Samples have a number of negative aspects, including personal use by prescribers and their families, creation of bias on prescribing habits for newer more costly agents, and inappropriate record keeping regarding delivered and dispensed samples (Pai, 2000). According to an American Medical Student Association report, the use of samples is associated with an influence on the prescription choices and behaviors of the physician (Vahia, 2007). Studies have demonstrated that the availability of free medications is considered by physicians when deciding upon a treatment regimen for a patient (Groves et al., 2003). Such an effect on physician prescribing behavior would most likely serve to sustain or expand the use of sampling practices.

Physician samples represent opposing forces with regard to medication waste. On the one hand, they can eliminate the dispensing of larger quantities of medication that may have gone unused. They also certainly do provide treatment and economic benefits to the patient. But on the other hand, they have the potential of being a significant source of unused pharmaceutical accumulation at the physician’s office or other healthcare facilities and have an important potential for drug diversion (US DOJ, 2006). Not only do the sample drugs remain unused and eventually expire in physician offices, they can accumulate in the possession of the patients as well. Physicians have no incentive to decline sampling, often accepting all that are offered during detailing. At the same time, patients have little incentive to decline the offer of free samples from the physician, even if they doubt they will ever use them. There is no requirement for physicians to maintain
an inventory and therefore, as opposed to pharmacies, there is no real measure of how many samples are required for the number of patients and types of maladies seen in a particular physician office. Consequently, samples will go unused and will eventually expire in the physician’s sample closet. Pharmaceutical representatives do not accept the return of the samples, so they must eventually be disposed of by the office. The disposal will most likely be via the trash because the packaging (which is usually of unit-dispense design) would impede easy and convenient disposal via the sewage system. Few published studies have assessed the extent of accumulation of expired sample medication or the means of disposal by physician offices. In a single Canadian study, the population of a single hospital was invited to return medications over a 2-day period, during which time 47 kg of medications were collected from 25 people (Nguyen et al., 2002). Over 87% of the wholesale value of the collected medications came from physician samples (valued over C$1,400 per physician); the bulk of these samples were medications for treatment of cardiovascular, CNS, and women's health. At least in one instance, the "Code of Marketing Practices" for Canada’s Research-Based Pharmaceutical Companies (Rx&D, 2004), guidance does exist for the disposal of "clinical evaluation package" (CEPs): "Companies are responsible for making sure that all excess and/or expired CEPs of their own manufacture are returned to the company’s storehouse or head office."

When samples are dispensed to patients they too may be destined for accumulation and eventual disposal. Samples are given so that a patient may “try out” a medication, often with unclear instructions. This unclear directive compounded by the distinct difference of a physician’s formal “prescription,” in that it is often given in random amounts, may prompt the patient to not necessarily consume as directed. In fact, sample
packages usually do not have directions on how to take the drug as opposed to the labels on dispensed medications. Patients may not understand how to properly consume the drug and may therefore be discouraged to use them. These unused drugs accumulate in household medicine cabinets and may be accessible to others for whom the medication might be contraindicated. While there is no research regarding the extent to which drug samples accumulate, local coroner data (Ruhoy and Daughton, 2007) here revealed the presence of unused sample packages with almost 5% of the decedents.

Long-Term Care Facilities

Pharmacists and other healthcare personnel employed by long-term care facilities (LTCFs) have expanded responsibilities with regard to dispensing pharmaceuticals to residents (and in disposing of leftovers). In addition to providing chronic maintenance medications on a daily basis to most, if not all, facility residents, personnel must be able to supply drugs in acute (i.e., pain control, agitation) and emergency situations (i.e., advanced cardiac life support), stock emergency medical kits for use by all facility healthcare personnel, and collect or receive expired, deteriorated, or recalled medications for proper disposal. Thus, pharmacy systems that cover LTCFs must maintain a different type and level of inventory than retail pharmacy locations. Because of the comprehensive distribution system, and by virtue of the quantities of pharmaceuticals required by this population, LTCFs are potentially an important source of accumulated and unwanted medication.

Driven by federal and state requirements and standards (Daughton, 2007), LTCFs often dispose of unwanted medications via sewage. There are presently a few studies underway to examine and assess pollutant discharge of these healthcare institutions,
especially from disposed pharmaceuticals. The US EPA Office of Water 2008 Effluent Guidelines Program (US EPA, 2008) aims to complete a health services industry survey on the disposition of unused pharmaceuticals in LTCFs, veterinarian offices, and hospitals. In an effort to understand the extent of discharge of pharmaceuticals into water and possible environmental effects, this study plans to request that these facilities submit data on the quantities and types of medications disposed, and the frequencies of disposal via the sink, toilet, or trash. Analysis of this information could eventually be used to inform a national standard for disposal and treatment of unused pharmaceuticals at these types of facilities.

Prison Pharmacy Services

In an effort to service the greater than 2.2 million prisoners in federal, state, and local incarceration facilities (US DOJ, 2005), prescription medications were the third largest healthcare cost for prison institutions in 2002, behind hospital care and physician and clinical services (DHHS, 1990). Pharmaceuticals for inmates are provided by either an on-site pharmacy at the particular facility or an outside pharmaceutical company that services correctional facilities. The private companies represent a “closed-loop” system in which they do not offer retail pharmaceutical services to the public or non-incarcerated individuals. This system is not different from the non-incarcerated public per se, but it is important in the sense that it maintains its own inventory and distribution system.

In an audit of the Federal Bureau of Prisons Pharmacy Services (US DOJ, 2005), prescription medication costs associated with waste were estimated at $2.81 million in 2004. This represented 2.54% of the Bureau of Prison’s total medication costs. Almost half of the cost associated with pharmaceutical waste was due to the transfer of inmates.
Transferred inmates are not required to take their medication with them to their new facility. These medications are often abandoned in an inmate’s cell or locker. In addition, upon transference, without regard to whether the inmate’s drugs have been sent along, an inmate automatically receives an additional week’s supply of each of their prescribed medications. The abandoned, unused drugs are disposed of since they cannot be recycled and dispensed to another inmate.

Another reason for discarded medications in the prison systems is from regular searches of an inmate’s belongings. Expired medications, and illicit drugs, are confiscated during these searches and then disposed. In addition, a Bureau of Prison’s policy states that medications are only valid 90 days from date of issue, regardless of the manufacturer’s expiration date. This results in more frequent and greater quantities than normal of drugs requiring disposal.

The categories of medications taken by incarcerated populations are dominated by anti-depressants. Research indicates that approximately one in seven prisoners in western countries have psychotic illness or major depression and a greater number suffer from more mild psychiatric illnesses, such as personality disorders (Fazel and Danesh, 2002). In a 2006 Bureau of Justice Statistics Special Report (US DOJ, 2006), it was estimated that at midyear 2005, greater than half of all inmates had a mental health problem, defined as major depression, mania, or psychosis. This assessment represented 56% of all state prisoners, 45% of all federal prisoners, and 64% of all local jail inmates. The report further indicates that 26.8% of state prisoners, 19.5% of federal prisoners, and 14.8% of local jail inmates were given prescription drugs to treat their mental illness. The frequency of prescribing of these drugs rose 3% from 1997 to 2004. While the report
does not specify which drugs were prescribed, most likely the drugs administered were anti-depressants, anti-psychotics, and benzodiazepines.

Household Medicine Cabinets

That drugs accumulate in the ubiquitous household medicine cabinet is common knowledge. The medicine cabinet usually serves as the focal point for organizations and agencies attempting to develop solutions for unwanted drug disposal. Obviously, the ultimate reasons for why drugs go unwanted and accumulate in the home are because consumers choose or are told to not consume the medication, or forget they have them. Why they choose to not consume the medications is varied and some reasons originate from the healthcare practitioner, some from the patient, and yet still others from the medication itself. As much as 60% of all medication prescribed is taken incorrectly, or not at all (NCPIE, 1995). This non-compliance includes behaviors such as forgetting to take the medication, deliberate under-dosing, and hoarding medications to take later (Figure 4). Medications that have the highest rate of non-compliance include gastrointestinal agents (84%), osteoporotic agents (82%), anti-arrhythmics (80%), pulmonary agents (80%), and Alzheimer's treatments (75%) (ScriptAssist, 2007).

Although the scope and magnitude of drug stockpiling in the home are largely unknown, coroner inventory data lend some insight as to the types and quantities that occur (see Chapter 2 and Ruhoy and Daughton, 2007). One cause of stockpiling is the large numbers of drugs (including OTC medications) sometimes stockpiled by addicts entering addiction recovery treatment (Lessenger and Feinberg 2008); these stocks must all be disposed of at once.
An emerging indicator of the significance of household medicine accumulation as a cause and source of drug disposal is the increasing implementation of unused-drug take-back events and programs in various states in the US. These take-backs are increasingly popular as a local means to collect and dispose of unwanted drugs, taking the responsibility out of the hands of the consumer. (In contrast to the US, many other countries have had large-scale consumer drug "returns" programs in place for quite some time; Daughton, 2003b).

At these local take-back events, organizers will often attempt to record some sort of measure of the quantities of medications that have been collected. Usually the measure is simply the bulk weight or volume of the complete medications (often including the packaging), providing little idea of the associated quantities of APIs. These bulk measures might be useful in roughly comparing the success of one take-back event to another but they provide little data relevant to environmental issues. The types and masses of each API are the salient data. Take-back programs could be designed to assess the categories and dosage amounts of the APIs being returned, but this requires substantial time, effort, and resources, as calculations must be made for every API in each type of medication (Ruhoy and Daughton, 2007). The work of Braund et al. (2007) is one of the few examples of detailed API-based cataloging that can be done at take-backs.

Regardless of their limitations, take-back events serve to highlight the need for prudent disposal of accumulated household medications. Each take-back event invariably collects numerous types of medications. For example, an event held in Sonoma County, California during November 2007 collected 128 non-controlled human medications.
during a 2-hour local event. An event held on June 9, 2007 in the city of Milwaukee collected 2,387 pounds, including some packaging, of non-controlled substances. This event, which was done in conjunction with law enforcement and therefore could accept the return of controlled substances, collected 985 controlled prescriptions. Group Health pharmacies in Seattle collected 2 tons of returned drugs from patients during approximately a one-month period (Ervin, 2008). These events and others are summarized by an Illinois-Indiana Sea Grant project (IISG, 2007). Many other medication disposal programs are underway in communities across the nation.

Take-back events also reveal the difficulties in organizing collections at the local level and perhaps the infeasibility of collections becoming a standard, sustainable method of removal of accumulated medications from households. Pharmacies are sometimes reticent to participate; law enforcement must be present to allow for collection of controlled substances; the public is encouraged to perhaps make trips that would otherwise not be made; and hazardous waste handling are required for ultimate disposal (via incineration or landfilling). These all impose monetary and labor costs and add to the environmental footprint of the overall process.

Perhaps more importantly, state governments are recognizing the need for guidance and regulation and are discussing the establishment of state product stewardship programs. Several states, such as Washington (HB 2600: http://wastenotwashington.org/HB2600summary.pdf), Maine (HB 411), Minnesota (HB 1959), and Iowa (IAS 579), have passed legislation that authorizes and guides some form of a pharmaceutical collection and disposal project. Other states, while specific legislation has not yet been enacted, have issued public guidelines and educational
materials. An example of such is the Guidelines for Proper Disposal of Household Medication issued by the New Jersey Department of Environmental Protection (http://www.state.nj.us/dep/dshw/rrtp/disposal.pdf).

Physician and Dental Offices

Beyond samples given to patients, physician and dental offices maintain particular inventories of pharmaceuticals on-site for intra-office procedures performed on patients. There are many types of procedures that can be done in the office or clinic setting, and the type of procedure performed depends on the medical or dental specialty of the office. The types of drugs needed for these procedures usually consist of anesthetics, analgesics, anti-pyretics, anti-microbials, steroidals, anti-inflammatory, immunosuppressives, and cardiovascular (which are usually reserved for emergency scenarios).

Although over time a physician or dentist might develop a reliable assessment of the quantities and categories of drugs that are necessary to have on-site so as to avoid having excess, each office inevitably has some level of expired drug or drug that is no longer required that needs to be disposed. The method of disposal historically has been sewerage, office trash, hazardous waste, or sharps disposal.

Veterinarian Offices

As described for physician and dental offices, veterinarian offices also maintain an onsite inventory of drugs for intra-office procedures. There are, however, two main differences. First, veterinary offices also serve as surgical centers for animals. So the procedures performed are more invasive and intensive and therefore often require at least greater quantities of most of the categories of pharmaceuticals required for human therapy (but often the APIs are unique and specific for veterinary use), as well as
additional categories and higher potency drugs; veterinary offices also employ unique
categories, such as medications for euthanasia. Second, veterinarian offices usually
maintain their own pharmacies for filling outpatient prescriptions. So they face the same
problems as do human consumer pharmacies. Veterinary offices that practice animal
euthanasia can inadvertently dispose of hazardous anesthetics by way of improper
disposal of carcasses, which can lead to acute poisonings of raptors and other scavengers
(Daughton, 2007).

Cruise Ships

Cruise ships generate and discharge multiple types of waste to the aquatic
environment, including sewage, graywater, hazardous wastes, oily bilge water, ballast
water, and solid waste (CRS, 2005). These wastes, if not properly treated and disposed
of, can be a source of aquatic contaminants with the potential to threaten human health
and damage aquatic life. While there are many other types of shipping industries that
generate particular waste streams, with regard to public consumption and use of
pharmaceuticals, cruise ships are the major source. A 2005 Congressional Research
Service (CRS) report on cruise ship pollution for Congress categorized pharmaceutical
waste from cruise ships as hazardous pollution (Copeland, 2005).

In 2000, a volunteer, independent science panel convened by the Ocean Conservation
and Tourism Alliance (OCTA) was asked to evaluate the management practices for cruise
ship wastewater discharges, and to recommend guidelines for good and improved
practices to the International Council of Cruise Lines (ICCL). Their report recognized
prescription and non-prescription drugs as a class of water contaminants of growing
concern and recommended the Council establish procedures that are congruent with the US Environmental Protection Agency's policies for waste disposal.

Waste generated from cruise liners has been recognized in the past. The ICCL set forth 2001 industry waste management practices and procedures in the ICCL Standard E-1-01 (Revision 3), revised in 2005 (Copeland, 2005). The Standard recognized that cruise ships store and carry various pharmaceuticals, depending on the destination and passenger population; they usually consist of both prescribed and over-the-counter medications. The document further describes particular handling methods: establishment of a reverse distribution system for returning unexpired, unopened, non-narcotic drugs to the issuing vendor, witnessed destruction of narcotic drugs, obeying state waste regulations for disposal of unused drugs aboard the ship at time of docking, and onboard incineration of other non-narcotic drugs.

Currently, there are no accessible data regarding the quantities or categories of the pharmaceuticals commonly onboard cruise ships and to what extent they go unused and are in need of disposal or return. However, the nature of the cruise line business is such that it would not be unexpected that a large amount of the drugs maintained onboard would go unused since they are only present for health-care exigencies with passengers. The onboard pharmacies are not intended to treat or manage chronic disease, but mainly to support acute medical needs of their passengers.

Abandoned Pharmaceuticals

Many of the sites and locations so far discussed may also be subject to the intentional or unintentional abandonment of pharmaceuticals by their intended user. For example, vacationers may forget to repack their medications after their cruise experience, and
children may bring their medicines to school and forget to return them home at the end of the day.

In addition, patients often have medications on their person when being admitted for a hospital stay but hospital policies dictate that the patient must use the medication administered by hospital pharmacy service and hospital personnel. This is to ensure safety and proper treatment for the acute illness, as well as any chronic illness the patient may suffer from. At the time of discharge, a patient will often forget to retrieve their medicinal belongings and effectively abandon these drugs at the hospital.

Perhaps more commonly are the drugs unintentionally left behind at various vacation spots. While there is no reportable data on the subject, hotels, motels, and lodges undoubtedly find and dispose of medications left behind from vacationers.

Armed Forces

The US Department of Defense (DoD) maintains its own pharmaceutical supply and distribution and its own process for return and disposal of unused medications to support and serve the military population. All DoD facilities, including the fleet, purchase pharmaceuticals from the Defense Supply Center Philadelphia (DSCP) prime vendor program. DSCP contracts with wholesalers to provide the drugs and delivery to the customers.

Expired, unopened, and unused drugs are shipped to contractors specializing in the recovery of credits for unused or unopened expired drugs and subsequently use those credits to replenish their stock. The military customers receive partial credit for the return of these drugs. Opened and unused drugs, on the other hand, are incinerated by licensed contractors, who contract with DSCP. If the drugs are considered hazardous or controlled
substances, the contractors are required to provide documentation of where and when the destruction took place. Classes and doses of the drugs are not documented. Because the military maintains its own closed and organized system, sewerage and landfill disposal apparently does not take place on a regular basis at military sites. While this system seems to not significantly contribute to the problem of the accumulation of unwanted medications, it is important to acknowledge the potential of its contribution. There are approximately 1.4 million active members of the military (http://www.census.gov/Press-Release/www/2003/cb03-ff04se.html). If there were no effective system for removing unused pharmaceuticals, the quantity of unused drugs that would potentially accumulate would be significant. It may be a helpful exercise to consider the implementation of the military system for unused medicine disposal in civilian sites as well. The ongoing DoD/FDA Shelf Life Extension Program (SLEP) performs testing on various products to effectively extend shelf life and thereby reduce the need for disposal (https://slep.dmsfbda.army.mil/portal/page?_pageid=33,220138&_dad=portal&_schema=PORTAL).

Coroner Offices

Coroner offices were recently shown to perhaps be the only ready source of data on drug disposal in the US (see Chapter 2 and Ruhoy and Daughton, 2007). They also represent a previously unrecognized source of disposal themselves. In this work is compiled a rich data set on the types, frequencies, and quantities of APIs found by medical investigators and then disposed into sewage. These data are particularly valuable because they represent known input for individual APIs over a defined time frame to particular sewage treatment plants (STPs). This allows calculations of influent
concentrations (averaged over time) for STPs. In Table 4, however, is presented some summary data showing the therapeutic-class distribution of nearly 400 distinct APIs that had been disposed to several known STPs over a defined period of time. This is the first time that a sufficiently rich set of data have been compiled to allow for meaningful categorization of data according to therapeutic class (according to the Anatomical Therapeutic Chemical system: ATC). A major unknown and point of debate is the extent to which disposal of medicines contributes to the levels of APIs detected in waterways, which is a function of the types and quantities of medications disposed, the route of disposal, the route of administration (topically applied drugs can be efficiently washed from the body and essentially serve as disposed drugs), type of packaging, and the extent to which any given API is metabolized (which dictates the relative contributions by excretion). An even greater unknown is the relative contributions of APIs among the various types of locations from which they are disposed. In order to properly examine this question, reliable and verifiable data are necessary for each of these variables. Historically, it has been difficult to determine what drugs, if any, were discarded into the toilet or trash, and in what absolute and relative quantities. The lack of information is mainly due to the absence of any reporting system. Historically, the advice from healthcare personnel and pharmacists has been to simply discard unwanted medications via the sewer or the garbage. This practice took place consistently and persistently without any perceived need to report or file information regarding the details of this behavior.
Conclusions

A frequent criticism of focusing on drug disposal as a source contributing to APIs in the environment is the lack of understanding of its overall significance — which is believed by many to be inconsequential. This is primarily a result of the absence of data regarding the types and quantities of APIs that are actually disposed during defined periods of time, coupled with a lack of appreciation for the many sources that contribute to disposed drugs. This data gap was the primary driver behind Chapter 2 which uses coroner inventory data to collect real-world disposal data from known segments of the population (see also Ruhoy and Daughton, 2007).

Regardless of what fraction of individual or total APIs in the environment originate from disposal of unused drugs, it is important to note that it is not just the quantities of APIs introduced to the environment that would be important with regard to their potential environmental impact. Also of importance, but rarely mentioned, would be any temporal or spatial characteristics of their release that differs from the continual but low-level releases resulting from intended use by the general population. Disposal holds the potential to introduce transiently high quantities of APIs into sewage (Daughton and Ruhoy, accepted 2008). These spikes in concentrations could lead to increased exposure for aquatic organisms, for example, should the APIs survive sewage treatment; it may be likely that risks could also be increased with respect to the homeostasis of the unique assemblages of microbial consortia that exist at each activated sludge sewage treatment facility.

There are several aspects unique to the purposeful disposal of drugs by flushing compared with the unintentional release (via excretion and bathing) of APIs resulting
from their designed therapeutic usage that could prove significant with respect to environmental exposure. These aspects serve as additional imperatives for ensuring that the disposal of drugs is environmentally sound.

The factors controlling drug wastage and leading to disposal are numerous, varied, widespread, and complex. Although this analysis could be used to ensure that the design of programs for collecting leftover drugs is better informed, approaches for leftover drug control such as local take-backs or other types of local “collections” may not succeed in efficiently capturing stored medications in a timely manner (to reduce accidental poisonings). These programs also have significant sustained costs. A preferred approach would prevent the accumulation (and need to dispose) of medications to begin with – an up-stream “green” approach to preventing pollution as opposed to a “down-stream” approach directed at controlling pollution. An effective and efficient approach aimed at pollution prevention would obviate the need for drug collection programs. Of significance is that a holistic pollution prevention approach could also potentially afford a number of advantages for healthcare, including improved therapeutic outcomes, reduced healthcare expenses, and lower incidence of drug diversion (which facilitates abuse and poisonings of humans and animals). The accumulation of medications is a rare instance where human health and safety is linked directly with environmental integrity. These ideas are embodied in what is termed pharmEcovigilance (Daughton and Ruhoy, 2008).

Take-back events, however, do have the potential to contribute substantial data relevant to the general population. Take-backs can be held in just about any geographic area under the appropriate circumstances. They can also be held indefinitely, for as long as the organizers are able and willing to participate. These events have the distinct
advantage of surveying the consumer and inquiring as to why the medicine accumulated as well as other parameters regarding the history of the use and non-use of the medication. These drugs can be categorized and counted, and the information can be compiled in a database. As mentioned earlier, these events usually simply record the weight of the entire collected medication, which often includes packaging. While weight can be useful to compare one take-back to another, it does not provide information regarding the constituent APIs. Another major limitation of data collected from take-backs is that it does not necessarily represent the frequency or rate at which drugs would be disposed on a sustained basis (because consumers often stockpile their medications over long periods of time for one-time disposal at take-back events). Considering the importance of this information, a standardized methodology for collecting data from take-back events or returns programs would be useful to environmental scientists, to the healthcare and insurance industries, and to regulators. For future studies, a recommendation would be that data for APIs from collected drugs be coded according to therapeutic class (e.g., using the Anatomical Therapeutic Chemical [ATC] system: http://www.fmrc.org.au/atc/index.htm), which would greatly facilitate the sharing and intercomparison of data.

By categorizing the coroner drug-disposal data collected by Ruhoy and Daughton (2007, unpublished) using the ATC system, it becomes immediately clear that the bulk of the API mass disposed (>94%) represented only five of the 14 ATC therapeutic categories: Alimentary Tract, Nervous System, Cardiovascular System, Anti-infectives, and Musculoskeletal System (Table 2). The other nine categories therefore were negligible contributors to the total mass of APIs introduced to the environment by the
coroner; considerations of potency would need to be evaluated, however, to eliminate these categories as contributors to overall hazard in the aquatic environment.

The major opportunities for pollution prevention are discussed. These opportunities are based on minimizing the types and quantities of drugs dispensed to consumers (or how they are made available OTC) as well as altering the consumption and behaviour patterns of consumers. Unit dispensing, as opposed to bulk dispensing, has the potential to deliver the correct dosage of drug at the correct timing. Already in widespread use in healthcare institutions, such as hospitals and LTCFs, unit dosing not only has the potential to reduce the inventory of medications in a patient's possession, but can also reduce medication errors – whether it is the amount or time of consumption. To perfect a method of unit dosing in the retail market may be a perceived obstacle, but technologies already exist regarding unit dose re-packaging (e.g., see: Parata Systems: http://www.parata.com/adhere/index.php) suitable for use in doctor offices and pharmacies. At a minimum, low-quantity prescriptions coupled, if needed, with more frequent refills could be encouraged when the need for an ongoing course of treatment is not clear, especially when longer-term (e.g., 90-day) prescriptions are being considered.

Trial prescription periods and increased monitoring of patients can only have the benefit of improved health outcomes, improved physician-patient relationships, and a reduction in the quantities of unused, unwanted, ineffective, and expired medications. Identifying poor compliance and reasons for lack of adherence will help healthcare personnel to adjust treatment or to better counsel the patient accordingly. In addition, identifying good compliance can serve to allow the healthcare team to assess
effectiveness of treatment and adjust as necessary. These steps will assist in reducing the accumulation and eventual disposal of unused medications.

The information and evaluation provided here could be used to design the framework for a holistic pollution prevention program for medications. Such a program would serve an integral role in pharmEcovigilance as conceptualized by Daughton and Ruhoy (2008). Designing an effective program will also afford the unusual opportunity for collaborations among professionals from the healthcare and environmental science communities, which could yield various unanticipated beneficial outcomes.

Numerous factors play roles in the accumulation of drugs by end-users, whether they are healthcare professionals, physicians, patients themselves, veterinarians, farmers, or humanitarian relief workers. Expiration of prescribed drugs is a reason for accumulated drugs, but numerous other factors play significant roles, including patient non-adherence and over-prescribing or excessive purchase; these have been summarized by Daughton and Ruhoy (2008). Poor adherence and non-compliance continues to be a major public health concern (NCPIE, 2007). Significantly, the number of consumers who do not follow medication regimens in the US continues to be substantial, and addressing the causes could improve therapeutic outcomes and reduce morbidity and mortality.

Patients will imprudently discontinue medications for a wide variety of reasons, including adverse effects, the perceived absence of beneficial effects, inconvenience in dosing schedules, change in therapy as prescribed by their physician, or even a poor perception of the severity of their illness. See Pound et al. (2008) for an in-depth discussion of compliance.
Sites where wasted drugs accumulate extend well beyond the household medicine cabinet. Some drugs are simply forgotten by consumers at a distant location (i.e., hotels, workplace, and hospitals), some are lost track of (e.g., when stored in obscure, alternative places to secure them from others), and some are intentionally abandoned. Physician, dental, and veterinary offices have supplies of drugs on hand for intra-office procedures and sample dispensing. However, some areas of substantial drug wastage are independent of the individual consumer as a patient. These locations are associated with the demands and expectations of the public for the easy accessibility and availability of medications should they be needed. Public buildings, vacations areas and maritime vessels, and societal institutions such as prison systems and military bases are all locations where drugs are stored in large quantities in case the need arises. This ready-as-needed approach maximizes the chances that the medication will not be needed, eventually leading to expiration and the necessity for their disposal.

The flow chart in Figure 3 represents an overview of the various locations where drug buildup and eventual disposal may prove to be significant. It begins with the actual production of the pharmaceutical and traces the many places in which a drug may end up following its purchase, either by prescription, OTC, importation from a foreign country, illegal web-based pharmacy, or by other means.
<table>
<thead>
<tr>
<th>ATC Code</th>
<th>ATC Main Group</th>
<th>Quantity (mg) disposed</th>
<th>#of APIs</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Alimentary Tract</td>
<td>18,685,27</td>
<td>56</td>
<td>34.6</td>
</tr>
<tr>
<td>N</td>
<td>Nervous System</td>
<td>16,510,96</td>
<td>95</td>
<td>30.6</td>
</tr>
<tr>
<td>C</td>
<td>Cardiovascular System</td>
<td>6,331,976</td>
<td>71</td>
<td>11.7</td>
</tr>
<tr>
<td>J</td>
<td>Anti-infectives</td>
<td>5,608,735</td>
<td>45</td>
<td>10.4</td>
</tr>
<tr>
<td>M</td>
<td>Musculoskeletal System</td>
<td>3,851,949</td>
<td>21</td>
<td>7.1</td>
</tr>
<tr>
<td>R</td>
<td>Respiratory System</td>
<td>984,780</td>
<td>16</td>
<td>1.8</td>
</tr>
<tr>
<td>B</td>
<td>Blood</td>
<td>721,450</td>
<td>9</td>
<td>1.3</td>
</tr>
<tr>
<td>V</td>
<td>Various</td>
<td>622,800</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>P</td>
<td>Antiparasitics</td>
<td>236,269</td>
<td>2</td>
<td>0.44</td>
</tr>
<tr>
<td>L</td>
<td>Antineoplastics</td>
<td>186,013</td>
<td>14</td>
<td>0.34</td>
</tr>
<tr>
<td>G</td>
<td>GenitoUrinary/Sex Hormones</td>
<td>146,440</td>
<td>23</td>
<td>0.27</td>
</tr>
<tr>
<td>H</td>
<td>Hormonal Preparations</td>
<td>50,601</td>
<td>10</td>
<td>0.09</td>
</tr>
<tr>
<td>S</td>
<td>Sensory Organs</td>
<td>4,375</td>
<td>1</td>
<td>0.008</td>
</tr>
<tr>
<td>D</td>
<td>Dermatologicals</td>
<td>3,420</td>
<td>3</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>53,945,04</strong></td>
<td><strong>367</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Summary of API Masses Disposed to Sewerage by a Coroner Office during a 12-Month Period*: Categorized by Therapeutic Class*

*Data acquired January-December 2005 from Las Vegas, NV, with a resident population of approximately 1.8 million, and annual visitors of over 38 million.

Given the thousands of APIs in commercial use for treating a wide spectrum of conditions in both humans and animals, it is critical to have a framework that organizes this expanse of potential environmental chemical stressors in a standardized way that enhances communication and exchange of data among scientists and also the healthcare communities. There are two systems in wide use for categorizing drugs, primarily for the continual studies that surround drug utilization. One of these, adopted for the study here, is the Anatomical Therapeutic Chemical (ATC) system.
(http://www.fmrc.org.au/atc/index.htm), which is most commonly used outside the US but has the advantage in that it uses a more detailed hierarchical system that allows better distinguishing between closely related drugs. The ATC system parses all drugs into 14 different major groups (excluding an “other” category) according to the primary organ or physiological system for which they are prescribed; more detailed, lower levels in the hierarchy classify according to their chemical or pharmacological properties (such as mode or mechanism of action). An analogous system (ATCvet) is in place for veterinary drugs. The ATC system is maintained by the WHO Collaborating Centre for Drug Statistics Methodology. Every medication is classified according to its primary therapeutic use – classifications composing 14 primary anatomical groups (including the category ‘various’ and an additional 15th category for veterinary drugs), followed by succeeding detailed subgroups. Every API is listed by only one name – the International Nonproprietary Name (INN), which is the official non-proprietary or generic name assigned by WHO to each API (http://www.who.int/medicines/services/inn/en/). An analogous classification system (ATCvet system: http://www.whocc.no/atcvet/database/) is in place for classification of veterinary medicines. For most APIs, the ATC code is used to classify a veterinary product; in these instances, the ATCvet codes are created simply by placing the letter Q in front of the ATC code; new ATCvet codes are created only for veterinary products whose indications cannot be mapped onto analogous human APIs.
<table>
<thead>
<tr>
<th>UNIT DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimizes the quantity dispensed. The evidence that it improves patient adherence (and therapeutic outcomes), by ensuring that it will be consumed (and that wastage thereby minimized), may be at best marginal (Larsen and Haugbølle, 2007) but still equivocal (Connor et al., 2004); this is an important area for further investigation to further elucidate its potential benefits.</td>
</tr>
<tr>
<td>Ensures proper dosing for optimal healthcare outcome. Automated unit dose on-demand dispensers have been expensive and only suited to healthcare within facilities. But new technologies are becoming available; as one example, see: Parata Systems: <a href="http://www.parata.com/adhere/index.php">http://www.parata.com/adhere/index.php</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRIAL SCRIPTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allow for management of ineffective treatment, adverse effects, or poor compliance. Necessary before prescribing multi-month supplies.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOW QUANTITY PACKAGING OF OTC MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lessens chance of expiration. Allows consumer to experiment before deciding whether a larger quantity is warranted.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INCREASED MONITORING OF PATIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve patient care and health status by assessing effects of treatment on both disease and patient’s disposition. Helps to identify compliance issues early in treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMPLEMENT PRACTICE OF CONCORDANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The concept of concordance was developed in the UK. Its thrust is to actively involve the patient in the treatment process, developing mutual trust with the intent of improving compliance (Pound et al. 2005); actions include selecting medication and</td>
</tr>
</tbody>
</table>
dose to minimize side effects (and clearly explaining potential side effects and what to do to reduce their occurrence); minimizing numbers of medications; simplifying dosage regimens; allowing patient to make adjustments to therapeutic regimens (e.g., self-regulation). Indeed, involving the patient seems to be a major avenue toward improving patient compliance (van Dulmen et al., 2008). Interaction with the patient (especially when multiple physicians are involved) is one of the only ways to understand the extent of polypharmacy, a concern that continues to grow (Gorard, 2006).

<table>
<thead>
<tr>
<th>TABLE 3: MAJOR OPPORTUNITIES FOR PREVENTING THE WASTAGE AND ACCUMULATION OF MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREE SAMPLES AND DONATIONS</td>
</tr>
</tbody>
</table>

Types and quantities maintained at healthcare facilities can be carefully evaluated for need prior to acceptance. Assess the patient’s dedication to actually using the samples before providing them. Note that physician samples can be donated to charitable institutions by licensed practitioners if the samples meet certain criteria (e.g., expiry, packaging) set forth in CFR Title 21 (CFR 200). The barriers to donation of leftover drugs by consumers are covered by McKee (2006). Various state legislation pertinent to drug reuse has been proposed or passed since 2006 (NCSL, 2008).
### EPISODIC RELEASE

Release by disposal from just one or a few individuals might result in brief, episodic, transient spikes in concentrations of APIs in sewage – significantly higher than the more constant “ambient” levels resulting from the more continual, low-level release of APIs via excretion from numerous individuals living in communities served by the same sewage treatment plant.

### TYPE OF API

The types and quantities of APIs released by disposal will favor certain drugs compared with their release by excretion/bathing. One example is those drugs subject to abuse and which are recommended to be disposed via flushing. Another example is those medications that have universally poor compliance rates (e.g., anti-depressants).

### BYPASSING ADME

Disposal by flushing of those APIs that would otherwise undergo extensive metabolism before excretion could be a significant source for these particular APIs in the environment. The disposal of one dose of carbamazepine (CBZ), for example, could contribute the mass of CBZ in the environment comparable to what would result from roughly 29-87 ingested doses (calculated from data in Ruhoy and Daughton 2007; see Chapter 2).

### TIMING OF DISPOSAL
The times of drug disposal can be “compressed” compared with those for excretion/bathing. Certain locations (such as LTCFs) often dispose of drugs en mass on particular days or times of day after certain quantities have accumulated. A confluence of similar facilities (such as LTCFs) that practice routine drug disposal – and which the same STP serves – could amplify episodic releases. The season of the year could also make disposal more significant when those medications that tend to be taken during certain seasons are disposed during seasons when their usage is lowest.

<table>
<thead>
<tr>
<th>LOCATION OF DISPOSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain drugs are used disproportionately at certain locations (e.g., antipsychotics at LTCFs). A confluence of similar facilities (such as LTCFs) that routinely practice drug disposal and which are served by the same STP could amplify episodic releases.</td>
</tr>
</tbody>
</table>

Table 4: Unique Aspects of Drug Disposal via Flushing (in Contrast with Excretion/Bathing) that Could Prove Environmentally Significant
Accumulation and Disposal of Pharmaceuticals
IS RuhoY & CG Daughton
U.S. EPA-Las Vegas
15 December 2006
(rev 15 May 2008)

Figure 3: Accumulation and Disposal of Pharmaceuticals
Figure 4: Factors Influencing Drug Consumption
References


CFR. Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department of Health and Human Services, Subchapter C—Drugs: General, Part 203—Prescription Drug Marketing, Subpart D—Samples, § 203.39 Donation of drug samples to charitable institutions; 2008. Available: http://eear.gov/cgi/t/text/text-idx?c=ecfr&sid=ec1033dbd03546f7dc73a2d35c683a6c&rpn=div8&view=text&node=21:4.0.1.1.4.1.10&idno=21 [Accessed 28 April 2008]


Larsen AB and Haugbolle LS. The impact of an automated dose-dispensing scheme on user compliance, medication understanding, and medication stockpiles. Res Social Admin Pharm. 3(3):265-284; 2007.


Overview

The fate of unused pharmaceuticals is poorly understood, although the issue has received increasing attention over the past several years. As argued in chapters 2 and 3, households are a critical point at which substantial quantities of a variety of pharmaceuticals accumulate. These accumulated pharmaceuticals are susceptible to undesirable exposures, including accidental misuse, intentional misuse/abuse, unauthorized transfer to a third party (e.g. dropping off controlled substances at a pharmacy or sharing with a family member or friend), and environmental exposure through illegal dumping or disposal to municipal sewers or landfills. Reducing the transfer of pharmaceuticals from households to inappropriate locations requires an understanding of the factors that promote or minimize acquisition, accumulation, and inappropriate use or disposal. Certainly, the efforts to reduce accumulation and inappropriate transfer may influence alternative behaviors. Potential undesirable outcomes include inadequate medication, a transfer of unused pharmaceuticals from one inappropriate disposal to another, and illegal disposal behavior. However, with proper monitoring these unfavorable behaviors may be mitigated or avoided.

Chapter two presented some novel data on the contributions and types of pharmaceuticals that accumulate at households, based on data from the Clark County
(Nevada) Coroner’s Office (see also Ruhoy and Daughton, 2007). Chapter three cataloged the reasons for, and locations of, accumulation of pharmaceuticals in the US, and evaluated the role of a pollution prevention approach to reducing those accumulations (see also Ruhoy and Daughton, 2008). This chapter takes a risk management approach to further develop the pollution prevention strategy used in chapter three for the case of household accumulation of pharmaceuticals.

The risk management perspective is particularly helpful in addressing tradeoffs. Risk management, which is practiced by everyone from insurance agencies to the Department of Homeland Security, distinguishes between the likelihood that things—good or bad—will happen, and the extent of the consequences of those good or bad things (see Kammen and Hassenzahl, 1999; Hassenzahl and Finkel, 2008). For example, it is true that if all the landfills in the US were flooded at the same time, a massive environmental release of pharmaceuticals would ensue. But this is so extremely improbable that it is not a scenario worth considering. The risk perspective can be useful to frame possibilities, and as one-way to help distinguish among different and effective management strategies.

Central to this approach is to understand the likelihood of various behaviors, practices, and impacts, and the consequences, whether harmful or beneficial, associated with those behaviors, practices and impacts.

Outlined here are the key drivers of household accumulation of unwanted pharmaceuticals, strategies for reducing such accumulation, and potential unintended consequences of changes to those drivers. Reducing undesirable exposures can best be accomplished through a strategy that integrates improved prescribing practices, information for consumers about prescription compliance and appropriate disposal,
clarification of legal disposal options, and changes to chain of custody that allows and regulates return of unused pharmaceuticals to points of purchase. Implementing this strategy would require cooperation among a range of agencies, including the Department of Justice, the Food and Drug Administration, the Environmental Protection Agency, and the Centers for Disease Control.

Introduction

That pharmaceuticals and their active ingredients exist in our environment, particularly our waterways, is now undisputed. The interpretation of their existence, however, with regard to risk of detrimental effects on human and ecological health, is poorly understood. Examined and assessed here is the transfer of pharmaceuticals from intended and appropriate locations to unintended and inappropriate locations. Prospective options for reducing those transfers and the potential impacts of those transfers are explored. Finally, opportunities for additional research on accumulation and transfers that would most likely reduce future needs for disposal are proposed.

The presence of pharmaceuticals in the environment is the focus of an ongoing dialog among private industries, the public, and governmental agencies. The US market accounts for 47.7% of global pharmaceutical sales (IMS, 2006). This lion’s share of drug use has not been without consequence. Concentrations of active pharmaceutical ingredients (APIs) have been detected in multiple water systems throughout the country (Daughton, 2001; Kolpin, et al. 2002; Fent et al., 2006) and have been the subject of recent local, national, and global media headlines. Researchers in a variety of fields continue to assess, analyze, and decipher the extent to which these compounds exist, and
why they exist, in the nation's water. Law and policymakers (Crow, 2008) are anxious to understand the issue and enact regulations that would serve to not only protect the public but address public fears (i.e., SB 966, 2007; MA 2182; HB 3064, 2008). In April 2007, the US Senate held a hearing to review federal efforts to assess and regulate drinking water contaminants, specifically pharmaceuticals (Argent & Schuster, 2008).

Primary treatment of disease and illness with the use of pharmaceutical medication has increased steadily over the past few decades. A 2007 study by Medco Health Solutions, Inc. demonstrated 51% of American children and adults were taking one or more prescription drugs to treat a disease diagnosed as chronic, or long-term. Since this does not correspond to a similar increase in the diagnosis of chronic conditions (Medco Health Solution, 2008), by implication, physicians increasingly turn to pharmaceuticals to treat and manage ailments. This increase in drug consumption would be expected to parallel an increase in the presence of pharmaceutical residues in our water.

The presence of APIs in the environment results from two major sources: excretion (and bathing) and disposal. The extent to which each contributes to the relative concentrations detected in water systems is unknown and difficult to assess (see Chapter 2 and Ruhoy and Daughton, 2007). Excretion of any particular medication depends on that drug’s pharmacokinetic profile, as some drugs are extensively metabolized, some are metabolites or biotransformation byproducts that may have biological activity similar to the parent API. The metabolic and physiologic profile of the consumer is another important factor in the subsequent excretion of the consumed drug. In most cases, proper consumption and natural excretion of a required medication are desired for beneficial therapeutic outcomes. However, optimal prescribing patterns and patient compliance may
reduce the quantity of medications that remain unused (see Chapter 3 and Ruhoy and Daughton, 2008). They may as well reduce the level of consumption of medications and, by extension, the quantity of compounds excreted. Regardless, discarding pills directly into sewage systems releases a much higher concentration of drugs into the environment than does excretion (Reid, 2007).

Disposal and removal of unwanted drugs can occur through household wastewater (toilet and sink), landfill sites (trash), or diversion practices, sometimes referred to as “pharming”. These three pathways for unwanted drugs are inappropriate transfers. Another major route – disposal (or amendment) of biosolids on agricultural land, as is currently the accepted standard method is another potential inappropriate transfer. Pharmaceutical residues have been measured in landfill leachate and therefore have the potential of entering the wastewater systems as well (if the leachate is transferred). The frequency and quantity of drugs that are discarded through either system in the US is an open question and an area of much needed research.

The predominant method of disposal of unwanted pharmaceuticals, based on small surveys both in the US and England, is via household waste and primarily in the trash (Bound and Voulvoulis, 2005; Kuspis and Krenzelok, 1996). Chapter 2 explored the quantities and categories of drugs discarded, mostly by flushing, by a local coroner office. The study demonstrated greater than 102,000,000 mg (102 kg) of various APIs disposed in a thirteen-month period for a population of approximately 2 million. To further elucidate the extent to which unused pharmaceuticals are discarded, the USEPA's Healthcare Industry Survey is a current project designed to characterize medication accumulation and disposal in long-term care facilities (US EPA, 2008).
The safest method of disposal for unused pharmaceuticals remains unclear. The desire to prevent drug residues in the environment can often be in conflict with the inherent need to protect public health. Wasted pharmaceuticals that remain in households or other potential areas of accumulation (see Chapter 3 and Ruhoy and Daughton, 2008) are readily available to those who seek to misuse, divert, or abuse these medications. Prescription drug diversion and the non-medical use of these medications is a current public health and safety concern (Inciardi et al., 2007; Lessenger and Feinberg, 2008).

Rates of abuse of prescription and over-the-counter medications (OTC) among teenagers are very high. Use of hydrocodone, for example, by teens for non-medical purposes has been reported for almost 10% of 12th graders (Keuhn, 2007) in the US. These drugs are also accessible for the potential of accidental poisonings. Deaths due to overdoses were reported in significant frequency in death certificate data (Wysowski, 2007). Deaths from medication mistakes at home increased from 1,132 deaths in 1983 to 12,426 in 2004 (Johnson, 2008). This concern fostered the 2007 federal guidelines for disposal of unwanted medication. These guidelines recommend the disposal of drugs into the trash, after first adulterating them, although the APIs remain in their original chemical state, and sealing them in a container. A list of drugs with a greater propensity for diversion was included with the recommendation for toilet disposal (ONDCP, 2007).

The risk to human morbidity and mortality from exposure to environmental concentrations is an area of active investigation and conversation. Kidd et al (2007) demonstrate that aquatic flora and fauna are susceptible to, and possibly adversely affected by, pharmaceutical contaminants. Medicines designed for human use may induce physiological and pathophysiological effects in aquatic organisms since receptor proteins
are shared among species, β-adrenergic receptors, for example (Owen et al., 2007).
Detrimental effects on wildlife of drugs at concentrations lower than 0.1 ng/l has been
demonstrates (D’Ascenzo et al., 2003; Warner and Jenkins, 2007; Boxall, 2004). Human
exposure to pharmaceuticals through environmental exposures is difficult to assess.

Human exposure to therapeutic doses is obviously not the concern. Aquatic exposure
rates are at least 100 fold lower than those required to produce minimal therapeutic
effects in humans (Kostich and Lazorchak, 2008) and environmental and human health
risk assessments seemingly demonstrate no appreciable immediate adverse effects to
aquatic environments (Winter MJ et al., 2007) and humans (Schulman et al., 2002;
Schwab et al., 2005; Daughton, in-press) from exposure to low concentrations.

However, chronic, low-level, involuntary exposures to multitudes of APIs may pose a
potential risk to human health (Collier, 2007; Daughton, in-press), particularly to
vulnerable populations (Filby et al., 2007), such as neonates (Grandjean et al., 2007).
Pharmaceuticals are designed to be biologically active at very low concentrations and are
approved to treat a specified pathology, not the population at large. In addition, various
drug-drug interactions are well established in the human body and these interactions may
play a role in effects due to environmental exposures to pharmaceuticals as well.
Bioaccumulation and bioconcentration has yet to be quantified and may also result
exposure levels substantially greater than those measured in the environment (USGS,
2008).

Some APIs, or combinations of APIs, may present greater toxic concern than others.
Sanderson et al. (2004) established a predicted rank order of relative toxicity of four
classes of pharmaceuticals, while noting that all examined pharmaceuticals have possible
toxicity. In rank order (from most to least toxic) they are: sex hormones, cardiovascular agents, antibiotics, and anti-neoplastics. Some drugs demonstrate considerable mixture toxicity, such as additivity or synergy, in combinations with other drugs of the same class (Cleuvers, 2004), or of different classes (DeLange et al., 2006). Kostich and Lazorchak (2008) found mutagenic cytotoxic agents display cumulative toxicity and long-term effects that appear linearly related to dose. Mixtures of drug compounds at environmental levels were found to inhibit growth of human embryonic kidney cells (Thrall, 2006). These are important and relevant findings since APIs rarely appear in the environment as single agents (Focazio et al., 2008).

Discussion

A four-stage risk management approach

Risk management can be an effective way to deal with complex environmental problems. The following paragraphs introduce a 4-stage risk management approach, which is then applied to the management of household pharmaceuticals.

A risk management approach takes a broad perspective on exposures to, and effects of, a particular hazard. Morgan (1981) describes four alternatives for risk management: (1) alter the built or human environment; (2) avoid or modify exposure processes; (3) avoid or modify effects processes; and, (4) mitigate or compensate for effects. Understanding the process by which the risk takes place can effect minimizing the potential risk.

In the case of household accumulation of pharmaceuticals, the hazard analog is the transfer of unused pharmaceuticals from appropriate to inappropriate locations. An
“appropriate” location for pharmaceuticals refers to any location for which pharmaceuticals are intended and originally conceptualized, or safe and legal disposal endpoints for those that go unused. These locations include manufacturing and distributing centers, pharmacies, sites intended for use in case of need by different segments of the populations (Ruhoy and Daughton, 2008), and the consumer household prior to its directed and expected consumption.

“ Appropriateness” also includes a quantitative dimension. So while it is appropriate to have pharmaceuticals present in pharmacies and perhaps in physician offices, it is also important that the amounts of the drugs residing in these otherwise appropriate locations would be the minimal amount required to fulfill their intended roles – in other words, their “appropriate” roles.

"Inappropriate" locations, therefore, refers to those locations where pharmaceuticals reside without the apparent objective of intended use and consumption. In some cases, these locations may be similar to the locations deemed “appropriate” (indeed, a single location may simultaneously be appropriate for some pharmaceuticals yet inappropriate for others). Once drugs become unwanted or unusable, either due to expiry, intolerable effects, or patient non-compliance, they are considered pharmaceutical waste and their residence becomes an inappropriate location. In addition, excessive production and stock of otherwise “appropriate” locations, such as distribution centers, pharmacies, physician offices, and pharmaceutical representative inventory results in the presence of drugs in an “inappropriate” location since their supply is not met by patient demand. Finally, “inappropriate” locations would almost obviously include any site that may possess medications in an illegal, immoral, or unethical manner.
From the risk management perspective, dealing with unused pharmaceuticals can be conceptualized in four stages: (1) alter the ways in which pharmaceuticals arrive at accumulation location; (2) avoid or modify the extent to which pharmaceuticals that arrive are allowed to accumulate; (3) avoid or modify the extent to which accumulated pharmaceuticals are transferred from appropriate to inappropriate locations (or between inappropriate locations); (4) mitigate or compensate for the effects of unused pharmaceuticals once transferred to inappropriate locations. This discussion focuses mainly on the household medicine cabinet with some ancillary discussion points regarding other locations. “Medicine cabinet” here is a catchall phrase; medicines are stored in a range of locations within a household, and often in multiple locations within a single household.

Pharmaceuticals are designed to treat human maladies and their deliberate context is to be prescribed for a patient in order to alleviate symptoms, improve quality of life, enhance lifestyle, ameliorate disease, or prolong life. Once pharmaceuticals are unused and unwanted they are then technically in an inappropriate location even though it is possible they were originally appropriately located. This inappropriate location may place the public in danger as these drugs may be accessible and available for intentional misuse and abuse or for unintentional usage, including dermal and pulmonary exposure, as well as ingestion. From this inappropriate location, these drugs are inappropriately transferred to another inappropriate location, with potentially greater adverse environmental impact. For example, an unwanted drug may be transferred from the household, which exposes a limited number of people to its accumulation, to an area of broader exposure potential, such as natural systems.
Wasted drugs are disposed of either via household trash, toilet, sink; through accidental ingestion; or by intended diversion, that is, the inappropriate transfer to another for whom the medication was not prescribed. In the case of controlled substances, this final scenario would violate the Controlled Substance Act (CSA) enforced by the US Drug Enforcement Administration (DEA) that prohibits the transfer of all controlled medication beyond the prescribee, even a physician or a pharmacist. In addition, the diversion of these substances contributes to drug addiction, as these drugs are often re-sold to those who seek to misuse these prescription drugs. Even in the case of non-controlled substances, transference would violate FDA mandates (US FDA, 1988) and place untold number of consumers in danger as all medication has the potential to cause toxic reactions under certain circumstances.

In many locations, medications disposed into the toilet enter the sewerage systems. From there they are treated in the sewage treatment plant (STP) and eventually result in treated sludge dispersed on fields, treated sewage released into the aquatic environment, or treated sewage injected into the ground. It is important to note that raw sewage is also frequently released — on purpose and by accident. Therefore, the pharmaceuticals entrained in such sewage have the potential to result in exposures to both terrestrial and aquatic organisms. Indeed, reproductive, endocrine, development, and behavioral effects on aquatic organisms have been reported.

Medications disposed into the household trash are collected by municipal waste handlers and are eventually (if not diverted by pharming or wildlife) disposed in landfill systems or incinerated. While not directly injected into wastewater, these pharmaceuticals have the potential for long-term persistence and eventual transport into ground water.
Pharmaceutical compounds have been detected in leachate samples from municipal landfills (Barnes et al. 2004). Lee and Jones-Lee (1998) suggest that older landfills with liners have poor groundwater monitoring systems and are unreliable. The latest geoengineered landfills collect the leachate and either treats it on-site or it is transported to an STP. Either way, treated effluent is often discharged into receiving streams.

Pharmaceuticals that remain in the household are available for accidental ingestion and potential subsequent poisoning. Unintentional pharmaceutical poisonings of children results in tragic and unnecessary morbidity and mortality each year. In 2005, according to the American Association of Poison Control Centers (AAPCC), of the almost 2,500,000 human exposures reported, 64.5% were reported to be children under the age of 20 years and 50.9% under the age of 6. This group of children and adolescents also accounted for 9% of the 1,261 fatalities due to poison exposure. The majority of these pediatric and adolescent fatalities were the result of intentional exposures – suicide, misuse, and abuse – to drugs. Of the reported deaths in children younger than six years of age, 16 were known to be unintentional. Of the 14 medication-associated deaths, 13 were from exposures to prescription medication, 5 of which contained opioids.

Finally, pharmaceuticals that are allowed to accumulate in inappropriate locations are accessible to those who seek to misuse, divert, or abuse these drugs. According to the National Center on Addiction and Substance Abuse at Columbia University (CASA), between 1992 and 2003, while the US population increased 13% and the number of prescriptions written for non-controlled drugs increased 57%, the number of prescriptions filled for controlled drugs increased 154%. During the same period, there was a 90% increase in the number of people who admitted abusing controlled prescription drugs.
Alarming, there was a 203% increase among 12- to 17-year olds (212% by 2003) and a 78% increase among those greater than 18-years old (81% by 2003).

CASA reports that the 15.1 million Americans abusing controlled prescription drugs exceed the combined number abusing cocaine (5.9 million), hallucinogens (4.0 million), inhalants (2.1 million), and heroin (.3 million). The use of alprazolam, oxycodone, and methylphenidate by teens (ages 12 – 17) increased 212% between 1992 and 2003. In 2003, 15% of teens abused or were addicted to controlled drugs, with opioids, CNS depressants, and stimulants being the most frequently reported.

According to the Drug Abuse Warning Network (DAWN), in 2005 there were almost 600,000 visits to US hospital emergency departments due to non-medical use of pharmaceuticals (e.g., recreational or unintentional use). This represents a greater than 20% increase from 2004. Bentur et al. (2004) found 84% of deliberate self-poisonings in the study population involved pharmaceuticals.

The following paragraphs develop the key factors that determine the impact or importance of each of the four risk management stages for the case of household accumulation, as operationalized for the case of household pharmaceuticals. For each stage, some key factors, and their implications, are outlined in Table 7. The hazard in this case is defined as transfer from appropriate location to inappropriate location. For each of the four risk management stages, understanding the factors that determine whether that stage is more or less likely to increase impacts is worthwhile. A detailed comparison across the four stages, then, could clarify the relative economic and ethical advantages and disadvantages of different strategies to minimize such transfers. Such a comparison, however, is beyond the scope of this dissertation.
Stage one interventions are those that prevent medicines that are not going to be used from arriving at the household in the first place. It encompasses the conditions that lead to the presence of pharmaceuticals in household locations following the manufacture, distribution, prescribing, dispensing, and purchase. To the extent that pharmaceutical prescribing and purchase leads to pharmaceutical accumulation in the home, steps can be taken to reduce the ultimate quantities of drugs that go unused and accumulate in the home and then require disposal. These steps include alternative methods of managing disease, effective and efficient prescribing practices, and reductions in incentives for excessive purchasing. Many of these considerations fall under the "pollution prevention" concept discussed in detail in Chapter 3 and Ruchoy and Daughton (2008).

The strategy to manage stage two, which is the minimization of pharmaceuticals that will not be used, is to improve patient compliance and adherence with prescribed treatment regimens. Improved compliance may ultimately result in reduced quantities of drugs that go unused. However, it is important in considering this to simultaneously avoid encouraging patients to take medications that have been purchased but which turn out not to be useful, necessary, or to cause unintended effects.

Stage three considers strategies for prudent and safe methods of disposal of pharmaceuticals that inevitably go unused. This stage encompasses those steps that must be taken as a society to ensure proper stewardship of the products that are manufactured by producers as well as the products that are purchased by consumers. Central to this stage is to improve patient awareness of the need to appropriately dispose of unused pharmaceuticals, and of the opportunities for appropriate disposal options. To the extent that appropriate disposal options are not readily available, stage three will also include
adding or improving disposal alternatives. Bound et al. (2005) suggest that environmental awareness and the perception of risk may have a positive impact on the motivation of the consumer to follow prudent disposal recommendations.

Stage four involves means of lessening the impact of environmental and human fate of pharmaceutical residues, such as treatment technologies. It includes technologies to remove pharmaceuticals from water or landfills, law enforcement efforts to prevent pharming or resale of medicines, clinical treatment or remediation for harm caused, or financial compensation for harms.

Significantly, the use of the four stages is an organizing heuristic: in reality, there is not always a clear differentiation among the stages. Further, interventions at one stage might have ripple effects on other stages. For example, charging pharmaceutical companies a penalty if their products are found in the environment is a fourth stage intervention. However, expecting such penalties might lead those companies to take preemptive actions most under their control. They might develop new distribution practices (a first stage intervention), or develop take-back strategies (a second stage intervention). Thus, while the discussion here is couched in terms of the four stages, it will be important that these not become reified in future research or in policy applications of this research.
<table>
<thead>
<tr>
<th>Stage</th>
<th>General Case (Morgan 1981)</th>
<th>Specific Case</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Modify the natural or human environment</td>
<td>Modify likelihood that households will acquire pharmaceuticals that will not eventually be used</td>
<td>Develop alternative treatments&lt;br&gt;Change distribution practices</td>
</tr>
<tr>
<td>2</td>
<td>Avoid or modify exposure process</td>
<td>Modify likelihood that acquired pharmaceuticals will be used</td>
<td>Minimize non-compliance, and non-adherence&lt;br&gt;Promote appropriate consumption of prescribed pharmaceuticals</td>
</tr>
<tr>
<td>3</td>
<td>Avoid or modify effects process</td>
<td>Modify likelihood of successful transfer of unused pharmaceuticals to an appropriate location</td>
<td>Facilitate transfer of unused pharmaceuticals to appropriate endpoints&lt;br&gt;Recognize major routes of inappropriate transfer&lt;br&gt;Develop take-back programs&lt;br&gt;Educate patients on appropriate disposal options</td>
</tr>
<tr>
<td>4</td>
<td>Mitigate or compensate for effects</td>
<td>Modify likelihood that pharmaceuticals transferred to an inappropriate location will have an adverse impact</td>
<td>Mitigate impacts of unused pharmaceuticals that have been transferred to an inappropriate location OR compensate for those impacts.&lt;br&gt;Develop sewage treatment systems that remove pharmaceuticals&lt;br&gt;Charge fees to patients, pharmaceutical companies or others for inappropriate transfers</td>
</tr>
</tbody>
</table>

Table 5: Strategies to Abate the Risk of Transfer of Pharmaceuticals from Households to Inappropriate Locations
As an example, fluoxetine is a commonly prescribed selective serotonin reuptake inhibitor (SSRI) that has been detected in surface waters (Kolpin et al., 2002). It is used to treat patients with clinical and sub-clinical depression. Non-compliance for antidepressant therapy is particularly high, both because of the effect on mood and motivation of the disease and because of the nature of chronic medication use. Keene et al. (2005) estimated 54% of patients become noncompliant during SSRI therapy. Indeed, in the Clark County (Nevada) Coroner data alone, approximately 67,250 mg of fluoxetine were identified in the homes of the decedents for the 13-month study period.

Fluoxetine has been shown to cause growth impairment in frogs (Holmes, 2003), behavioural alterations in invertebrates (DeLange et al., 2006), and have the potential for toxicity to other aquatic organisms (Johnson et al., 2007). Fluoxetine is almost completely removed from wastewater influents with advanced technologies such as ozonation (Snyder et al., 2006), but may be less effectively removed during treatment with less advanced and older technologies, such as membrane bioreactor systems (Snyder et al., 2005).

Risk management strategies as outlined by the four stages and with regards to the example of fluoxetine, might consist of: (1) directing patient to alternative treatment plans for the depression, such as behavioral modification therapy, homeopathic and naturopathic remedies, or lifestyle changes, particularly patients with minor and not major depression; (2) increased management and follow-up of patient to assess and improve upon adherence to medication treatment plan; (3) educating patients on safe methods of disposal, whether these be guidelines by federal organizations, state-specific waste handling regulations, or locally available take-back programs or returns; and (4)
improved technology regarding the removal and transformation of fluoxetine and its metabolites in water as well as increased resources dedicated to study the effects of the unintended human exposure to fluoxetine in the environment.

First Stage

The first stage is the arrival (or not) at a household of pharmaceuticals that, for one reason or another, will not be used as intended (table 5, row 2). Stage one is where one can modify the likelihood that households will acquire pharmaceuticals that will not eventually be used. Management strategies minimize acquisition of pharmaceuticals that will not be used at households. The distinction between appropriate and inappropriate locations for pharmaceuticals must begin with the acknowledgment of the appropriate use and transfer of pharmaceuticals. Pharmaceutical designed for human use save lives and ameliorate symptoms so as to provide millions of people with an improved quality of life. They improve health outcome and many of these medications have prevented untold levels of human epidemics and demise. A relatively recent class of pharmaceuticals and one with expanding sales includes those designed for elective usage by the consumer for lifestyle purposes, such as cosmetic and aesthetic use. Elective usage implies not primarily directed by a physician but by the patient. This may lead to prescriptions that would otherwise not have been written.

Pharmaceuticals that are optimally and appropriately prescribed to patients are dispensed and ultimately arrive at appropriate locations, such as the consumer household. Chapter 3 (see also Ruhoy and Daughton, 2008) explored various methods physicians and pharmacists may use to help minimize wasted pharmaceuticals and therefore by extension the inappropriate transfer of medication to inappropriate locations. These
recommendations would serve to improve health outcomes and health care resource management as well. As the field of medicine progresses, physicians may be better able to tailor treatment regimens for genetic variants of individual patients.

Genetic medicine is quickly becoming an important emerging discipline in clinical medicine. The practice of pharmacogenetics utilizes individual genetic information to improve the efficacy of the treatment selected. “Rational drug design” (Yıldırım et al., 2007) would take into account individual and disease-specific protein targets for better treatment response. Tests to determine genetic variations and genetic profile are becoming increasingly popular and requested (Katsanis et al., 2008). As this practice improves and increases, the optimal treatment may be prescribed for a patient and this may not only improve compliance, but also will most likely minimize the quantity of medications prescribed and dispensed during the course of treatment.

Optimal prescribing patterns are complex to assess and even more difficult to implement. Optimal prescribing patterns would take into account not only the most effective medication in terms of biochemical and biophysical effects on the disease course of the patient, but also takes into consideration the behavioral patterns of that individual patient. The decision on what to prescribe can be based on many factors. For example, the consistence presence of drug samples influenced physicians to prescribe drugs that differed from their “preferred” drug choice (Chew et al., 2000).

Non-compliance with treatment regimens can have significant public health implications. It is not part of standard training for a physician to assess the probability of compliance by that patient and in any case, the information is not readily available. Literature on compliance studies indicates it would depend not only on the medication
and the disease being treated, but personality characteristics and socioeconomic factors of that patient (Ellis, 2000). Yet decreased accumulation of pharmaceuticals in appropriate locations would require an understanding of the probability of proper compliance by an individual patient. Otherwise, even the most effective and efficiently prescribed medication would ultimately go unused.

Regardless, it is important for physicians and other prescribing health care professionals to minimizing the transfer, or the arrival, of pharmaceuticals most likely to go unused to appropriate locations. Focusing on the household, there are many options for the reduction of this transfer, such as unit dosing, trial scripts, and reduction in the use of samples.

Second Stage

The second stage is the success or failure of patients to use prescribed pharmaceuticals as intended (table 5, row 3). Stage two is where one can modify likelihood that acquired pharmaceuticals will be used. Management strategies promote appropriate consumption of prescribed pharmaceuticals. Factors that reduce or increase the amounts of unused pharmaceuticals that accumulate and are therefore at risk of inappropriate transfer are varied. Most reasons focus on directed or undirected behaviors by consumers. Compliance with prescribed medication regimens is a problem most physicians face in their practice. There are many reasons why patients discontinue treatment. Some of these reasons are valid, such as intolerable effects or a change in severity/course of the disease process, and may even be physician directed, such as change in treatment plan due to adverse events or ineffectiveness.
However, often a patient will cease taking prescribed medication either partially or completely. The potential for non-compliance depends upon not only individual, and life choices they are confronted with, but also with the medication itself. Some medications require complicated consumption directions, either with frequency, timing, dosing, or co-consumption with other products, such as food or drug products. Other medications require knowledge of difficult delivery systems, such as inhalers or syringes. Finally, some medications result in expected, but adverse effects, which will likely lead to poor motivation on the part of the patient to consume the medication. Regardless, non-compliance and non-adherence will lead to accumulated drugs.

Compliance rates in the literature can range anywhere from 0% to 100%, depending on the patient, the disease under treatment or the treatment itself. Studies have identified particular personality traits that may have a higher incidence of non-compliance (Cohen et al., 2004). These traits are not always obvious during a typical physician visit and therefore may go unnoticed and unattended by the prescribing physician. Patients may also not recognize the severity of their disease and the importance of their medication to prevent and forestall further progression and morbidity.

Some disease processes themselves can present difficulties for the patient to follow treatment plans. Fatigue, myalgias, neuralgias, paralysis, and depression can all result from disease and may leave the patient unmotivated, or incapable, to access medication. It is not without surprise that there is a high non-compliance rate with anti-depressant medications.

Cessation of treatment can also result from physician-directed alterations in the treatment plan. Side effects, adverse effects, or intolerable effects of medication are often
valid reasons for exchanging the current plan for a new one, with the resultant leftover medication. Treatment can also be halted because the desired effects are not appreciable and the disease course requires intervention.

Third Stage

The third stage is the failure or success of consumers to transfer unused pharmaceuticals to appropriate locations (table 5, row 4). Stage three is where one can modify likelihood of successful transfer of unused pharmaceuticals to an appropriate location. Management strategies facilitate transfer of unused pharmaceuticals to appropriate endpoints. A range of technical, legal and informational constraints limit the available strategies at this stage. The term “appropriate” thus includes several dimensions, including whether the location is secure in the sense of minimizing release to humans and/or the environment, as well as whether it is legal to make the transfer. Likewise, consumers may have no or limited knowledge about which transfer endpoints are appropriate and which are inappropriate.

Locating, identifying, and quantifying accumulated unwanted pharmaceuticals in all locations beyond the household medicine cabinet and healthcare facilities would serve to prevent the eventual routine need for disposal of these expired and otherwise unusable drugs into the environment. A centralized system of inventorying and monitoring all systems and locations where pharmaceutical compounds are dispensed and distributed could ensure their proper collection and disposal.

Secure locations would ensure public and environmental safety. These sites would prevent both humans and pets from inadvertently or intentionally accessing unused drugs. Law enforcement organizations would be the ideal location for unwanted medication
storage. These sites are protected from the public, and at the same time staffed with personnel charged with protecting the public. Currently, police officers are permitted to confiscate pharmaceuticals that are seized during the act of apprehending criminals and during criminal investigations. Extension of this standard to include all areas of law enforcement, such as state and federal Drug Enforcement Administration personnel, to accept unwanted pharmaceuticals from their respective communities would offer sites for medication drop-off.

Since the CSA prohibits the possession of controlled substances by anyone other than the end-user, it is difficult to devise a strategy for a centralized storage of unused drugs since it is not feasible to consider only medications that are not controlled. Consumers often are not familiar with the medications they are prescribed much less whether they are considered controlled substances. Therefore, law enforcement would serve to protect the public from diversion by housing those substances most vulnerable to acts of crime and abuse. At the same time, environmental safety would be preserved, as pharmaceutical waste residues would be prevented from entering natural systems.

Collection events at locations such as pharmacies and government edifices are a good alternative for at least the collection of these drugs, if not final storage. The issues once again surround the enforcement of the CSA. If collection events can have law enforcement involvement, they may able to circumvent the problem of accepting controlled substances. Of note, the US EPA Office of Child Health and Protection has issued a grant to the University of Maine for a mail-back pilot program. Consumers are given envelopes with their prescriptions in which they return unused medications. These
drugs are mailed to the Maine DEA who collects and stores the medications for later
disposal by incineration after transport by reverse distributors.

While awareness is increasing thanks to many programs as well as media interest,
consumers are still unsure of what to do with their unused pharmaceuticals. Certainly,
some local areas are more active and have held well-publicized take-back events. Yet
nationally the public remains confused. There does not exist a consensus of a
standardized solution or a generally accepted method of disposal. Further research to
decide safe and prudent methods of disposal is warranted.

Fourth Stage

The fourth and final stage is the mitigation of and/or compensation for impacts of
pharmaceuticals that have been inappropriately transferred (table 5, row 5). Stage four is
where one can modify the likelihood that pharmaceuticals transferred to an inappropriate
location will have an adverse impact. Management strategies mitigate impacts of unused
pharmaceuticals so transferred or compensate for those impacts. Wide ranges of
strategies are effective here. For example, most pharmaceutical manufacturers have
stewardship standards and practices for their products. With some overlap of a stage three
intervention, Pfizer maintains a Global Environment, Health, and Safety Policy that
ensures contribution to “protect the natural and workplace environment by advising
purchasers and users...about the safe handling and disposal of our products (Pfizer,
2007)”. Bristol-Meyers Squibb acknowledges recent reports of the detection of
pharmaceutical residues in water systems (Bristol-Myers Squibb, 2008) and states the
company’s support of further research. Merck has issued a public policy statement
(Merck, 2007) promising continued collaboration with stakeholders to promote and
support research in understanding the environment impacts of pharmaceutical products. Indeed, working through the Pharmaceutical Research and Manufacturers of America (PhRMA), Merck and other pharmaceutical manufacturers, together with the US Fish and Wildlife Service and the American Pharmacists Association, support the “SMART DISPOSAL” program (US FWS, 2007) which strives to educate the public about proper use and handling of medications. An additional relevant note is the recent announcement by PhRMA of new guidelines regarding the interactions between healthcare professionals and pharmaceutical manufacturer representatives (PhRMA, 2008). These new guidelines are intended to remove the perception of influence on the prescription choices of the healthcare practitioner, an important overlapping factor for stage one interventions.

Resources should be directed for research and development of reducing the environmental impacts of existing pharmaceuticals without compromising their therapeutic efficacy, or identifying alternate compounds with equal therapeutic efficacy but less environmental impact. For example, Sanderson et al. (2004a) found modifying additives to be most toxic in risk assessment of approximately 4,500 compounds, which included several pharmaceutical classes and their adjuvants. They recommended reduced use of these additives as a way of potential pollution prevention.

The Food and Drug Administration (FDA) requires the preparation of an environmental risk assessments (US FDA, 1998) for most pharmaceuticals proposed for human use. However, current assessments only require short-term tests that measure how much of a compound is required to kill an organism outright or stunt its growth in a matter of days. Longer studies may prove more useful. Furthermore, preparation of this environmental assessment ordinarily is required unless the proposed action qualifies for a
categorical exclusion (US FDA, 2008). A categorical exclusion from an environmental assessment is applied for newly formulated substances that would neither increase the use of the active compound, increase the estimated concentration of the compound in the aquatic environment, nor would it change the distribution of the active compound, its metabolites, or its degradates in the environment. The rate of new molecular entities released into the market has decreased over the past decade (AP, 2007). Generic switches and new formulations of pre-existing APIs dominate new drug approvals. Therefore, it may be fair to conclude that fewer environmental assessments are being required for new drug approvals in recent years.

Crucial to understanding the likelihoods and consequences of potential impacts of inappropriately transferred pharmaceuticals is identification and quantification of ultimate accumulation hotspots (landfills, sewage treatment systems). Chapter 3 and Ruhoy and Daughton (2008) outlined many locations where unused medication may be found. However, here is no ready source of data that addresses the quantity and frequency with which these drugs are inappropriately transferred to these and other locations, without which proper disposal procedures cannot effectively be enforced.

Pharmaceutical compounds that do enter the environment eventually are presented for treatment at STPs. Advanced sewage treatments, such as ozonation, can effectively remove many, if not most, pharmaceutical compounds. However, not all STPs in the US have updated technology. Sewage treatment systems are resource intensive. They require a substantial investment of land, labor, and funds. Problematically, some compounds are refractory to even the most advanced technology. For example, Snyder et al. (2006) demonstrated greater than 90% removal of target compounds using ozonation. However,
meprobamate, an anxiolytic drug, and iopromide, tri-iodinated x-ray contrast agent, continued to be recalcitrant. Ying et al. (2007) found estrone and 17α-ethinylestradiol, both synthetic estrogens, to be persistent during different treatment technologies. Other studies by Snyder et al. (2007) demonstrate presence of several refractory compounds following different treatments, such as activated carbon and membrane bioreactors, but clearly display the efficiency of a multi-tiered treatment approach in the reduction of concentrations of pharmaceutical residues. Resources should be directed for research to upgrade and improve water treatment systems.

Crucial to effective mitigation/compensation is the understanding of the likelihoods and consequences of impacts from each pharmaceutical agent. An appropriate protocol evaluates the potential effects of chronic, low-level exposure, as well as some specified mixture toxicity tests to account for the high probability of exposure to multiple pharmaceutical residues. Cooper et al. (2008) were able to rank pharmaceuticals in terms of risk of exposure based on physical, chemical, and toxicological data. Cardiovascular, anti-microbials and central nervous system agents were highly represented.

Once signs and symptoms of exposure to environmental concentrations of pharmaceutical compounds are identified, first-line treatment will most likely take place in the office of a healthcare practitioner. Treatment should be directed at the disease process assessed on an individual basis. As discussed for stage one intervention, treatment should be prudently and efficiently chosen. Alternative forms of treatment for toxicant exposure should be developed and considered. A recent article by McCoy (2008) addressed the benefits of bentonite clay for treatment of pharmaceutical exposures.
Finally, inappropriate transfers do not only result in low-dose human or ecosystem exposures; another problem is the effects of intentional or unintentional transfer to persons other than the prescription recipient. Drug diversion and abuse can have substantial public health consequences (NDIC, 2008). Law enforcement, from the local to international levels, represents one management strategy. Their role includes preventing drug diversion and punishing those who commit drug crimes. Another mitigation measure is treatment of those who abuse and continue to seek drugs through criminal means. Strategies to mitigate this exposure include further training of law enforcement officials, increased funding of social welfare programs, and improved addiction services.

Conclusion

This chapter has outlined a broad risk management perspective on reducing the impacts of transfers of pharmaceuticals from households to inappropriate endpoints. The next steps for this approach include both developing the details of the risk management stages for households, as well as applying it to the other accumulation locations. Importantly, any future assessment that applies the four-stage risk management approach developed above should attend to the whole model in addition to its parts. The four-stage model is a heuristic, and sticking to it too strictly could obscure important feedbacks among the stages, and obscure the important dimension of time.

I have assessed existing conditions, as well as identified critical knowledge gaps, in the accumulation of unused pharmaceuticals in society. In addition, I have addressed the impacts and implications of various strategies to modify the accumulation environment. In the final chapter of this dissertation, I provide some brief conclusions about the ethical,
resource and policy implications of changing the accumulation environment and the
approach to prescription drugs.

References

Argent & Schuster. U.S. Senate holds April hearing on regulation of pharmaceuticals in
drinking water—review of recent federal efforts dealing with emerging
2008]


Buck LE, Geisler CC, Schelhas J, Wollenberg E. (Eds). Biological Diversity: Balancing
Raton, FL

Barnes KK, Christenson SC, Kolpin DW, Focazio MJ, Furlong ET, Zougg SD, Meyer
MT, Barber LB. Pharmaceuticals and other organic waste water contaminants
within a leachate plume downgradient of a municipal landfill. Ground Water

Bentur Y, Raikhlin-Eisenkraft B, Lavee M. Toxicological features of deliberate self-

Bound JP, Voulvoulis N. Household disposal of pharmaceuticals as a pathway for aquatic
contamination in the United Kingdom. Environ Health Perspec. 2005. 113(12):
1705-1711.

Boxall ABA. The environmental side effects of medication. Viewpoint. EMBO Reports.

Bristol-Myers Squibb. Pharmaceuticals in the Environment. Environmental Performance:
August 2008]

Chew LD, O’Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician
survey of the effect of drug sample availability of physicians’ behavior. J Gen

Cleuvers M. Mixture toxicity of the anti-inflammatory drugs diclofenac, ibuprofen,

Cohen NL, Ross EC, Bagby RM, Farvolden P, Kennedy SH. The 5-factor model of
personality and antidepressant medication compliance. Can J Psychiatry. 2004:

Collier AC. Pharmaceutical Contaminants in Potable Water: Concerns for Pregnant


Ruhoy IS and Daughton CG. Types and quantities of leftover drugs entering the environment via disposal to sewage - revealed by coroner records. Sci Total Environ. 2007; 388 (1-3): 136-147.


CONCLUSIONS AND RECOMMENDATIONS

Academia, the public sector and the private sector increasingly prioritize research into the potential impacts of pharmaceutical residues, and effective means of handling and discarding unused and unwanted medications. However, current data, information and models provide limited to guidance for improved management. This dissertation provides a foundation in terms of estimating types of releases, the range of accumulation locations in society and mitigation strategies including pollution prevention and a four-stage risk management approach.

Several areas of further research are critical to improving management strategies. First, additional research is needed into fundamental information about sources and quantities of accumulation and disposal. Second, considerable progress could be made in assessing the range of policy options for changing prescription, distribution and disposal / return practices.

Research is needed into the human behaviors that motivate physicians to prescribe medications, and patients to continue or discontinue medications that they have been prescribed. It will be incumbent upon society to examine these behaviors and motivating factors. Interaction between doctor and patient will probably require longer times in order for both parties to gain a better understanding of the intent and motivation of the other. Yet if we are able to use pharmaceuticals in the most efficient manner and not necessarily
as a primary and reflexive course of treatment, and if we could provide more information and more guidance for patients through their treatment course, it is very likely we can reduce the demand, the supply, and the subsequent accumulation of unused and unwanted drugs.

The environment withstands and sustains insult and injury as a consequence to human ends. Its resilience cannot necessarily be relied upon for generations to come. In the Tragedy of the Commons, Garrett Hardin states “it is clear that we will greatly increase human misery if we do not, during the immediate future, assume that the world available to the terrestrial human population is finite”. Humans and their activities should be curtailed so that the ecological resources on which humans rely but often dismiss will continue to be in an appropriate state of health to deliver those services. Just as physicians may counsel patients to make better health and life choices so that the body may continue to serve them into older age, humans as a species should consider care for their environment and ecological landscape in order for the ecosystem to maintain effective balance.

Human activities must be guided by ecological rationality (Roling and Jiggins, 2001). The proposed recommendations for the curtailment of pharmaceutical consumption and behaviors can be appraised using a framework devised by Garry Brewer (1973) as outlined by Lee (2001). Specifically, the recommendations should be assessed based on its conceptual soundness, technicality, ethical limitations, and pragmatism.

Finally, there are more questions than answers regarding the presence of, and our exposure to, pharmaceuticals in the environment. We do know that they are consistently and continuously prescribed, dispensed, and all too often not consumed as intended. We
do know these unwanted medications accumulate and find their way to an inappropriate location, ultimately the natural environment. There is probably danger to aquatic, amphibian, and terrestrial wildlife and there is potential risk to human health as well. Human health can be affected by both exposure to environmental contaminants and diversion, and subsequent misuse, of prescription drugs.

We don’t yet know to what extent the disposal of unused medication, as opposed to excretion, contributes to the pharmaceutical residues detected in water systems. Undoubtedly, both excretion and direct disposal result in pharmaceutical compounds in the water. However, consumption and disposal behaviors are more readily modifiable. Yet in order to justify diverting resources to help improve how we as a society prescribe, how we as patients consume and adhere, as we as producers become stewards of our product, and as we as consumers strive towards a more sustainable world through our actions, behaviors, and perceptions, we must research and collect information with regard to what drugs are accumulating at inappropriate locations, how often they accumulate, and how and when they are discarded.

As shown in chapter two, coroner offices are a ready source of information, but there are other opportunities for data collection as well, such as at the numerous take-back events and collection programs currently underway in cities across the nation or at healthcare institutions. The data will help us understand the drugs that most commonly remain unused, which will guide physicians, scientists, and policymakers in their efforts to curb the incidence of unused drugs and the presence of their residues in waters.

We are only beginning to investigate the role of prescribed drugs in our society and the result of their inappropriate presence. Pharmaceuticals as environmental pollutants
are regulated, but our limited understanding of their origins, quantities, fate and transport leaves us uncertain about how effectively we have done so. Without this assessment, policies to minimize the exposure cannot be implemented. Once the policies can be implemented, they must be enforced with constant vigilance.

In addition, pharmaceuticals as primary treatment for patients may have become, in many instances, more reflexive and reactive than practical. Health care practitioners and patients alike have been bombarded with advertisement and information about the use of medications at a rate much greater than any methodical assessment and consideration can take place. This has led to greater prescription rates, excessive purchasing, and, ultimately, greater accumulation and eventual disposal.

The risk of exposure exists, yet the consequence of that risk has not yet been delineated. Pharmaceuticals are designed to be biologically active at low concentrations and were intended for a specified population (e.g., those suffering from a particular disease process). Pharmaceuticals were not designed nor intended for consumption by an unspecified population or for inappropriate accumulation and inappropriate transfer to inappropriate locations. The risk to life in close proximity to, and therefore directly dependent on, river and lake water has been partly established but the risk of life up the food chain has been underestimated since the exposure of any particular compound has been found to be at very low concentrations, particularly in drinking water.

Exposure to therapeutic doses is not the concern. The concern remains that if inappropriate accumulation and transfer were to continue to occur unabated, the persistent exposure to low doses of a multitude of biologically active compounds over decades could potentially result in detrimental effects on human health, especially on
vulnerable populations such as infants and the immunocompromised. Methods of risk mitigation and abatement cannot be calculated until the risk of inappropriate accumulation and transfer is established.

Many groups and organizations are working diligently on deciding the most prudent means of disposal of unwanted medications. Methods of destruction are being investigated (i.e., Abburi et al., 2007; Snyder et al., 2006; Snyder et al., 2007), pilot collection events are taking place (i.e., IISG, 2007), and there is great discussion on what to instruct the consumer to do with inappropriately accumulated medication (i.e., US FWS, 2007). The excess of unused drugs needs to be dealt with, certainly. But the ultimate objective should remain no leftover drugs.

A complete absence of leftover drugs would require a concentrated effort to understand human behaviors and human genetics. A recent focus on health, nutrition, and lifestyle advocate the incorporation of organic, whole foods, and supplementation to help prevent disease. Personalized medicine would allow for the most effective medication prescribed, but also the most efficient dose. This would be in contrast to the generic and mass prescribing for all having a certain physical complaint, as dictated by the many medicinal algorithms currently used by health care practitioners.

Personalized medicine, sometimes referred to as medical genetics or pharmacogenetics, strives to identify within each individual the genetic makeup that may or may not make them not only susceptible to disease, as done with screening tests, but also to better predict the response to treatment. With a customized treatment strategy, a patient may be more apt to understand what the treatment is for and what improvements in their current health status they can expect. This would almost certainly improve
compliance. Enhanced prescribing patterns and superior consumption behaviors would lead to improve health outcomes and a healthier environment.

Environmentally safe and yet accessible and affordable methods of disposal for pharmaceutical ingredients is a generally accepted ideal, as is the idea that we need to protect public health. Less general but still compelling is the need to change our drug-centric healthcare system, and to understand more holistically the relationship between human health and the environment. Our ecosystem is subject to unexpected and sometimes surprising change because of unrecognized vulnerabilities. To evolve into a sustainable society we must closely examine our actions and our behaviors to evaluate the short- and long-term effects. We all play roles in our places in society, whether it is physician, policymaker, scientist, educator, consumer, or manufacturer. Each role has a responsibility and those responsibilities are not mutually exclusive. The final outcome will depend upon the intent of each role player and the extent to which each role is filled.

References


Hardin G. The Tragedy of the Commons. 1968; 162: 1243-1248.


VITA

Graduate College
University of Nevada, Las Vegas

Ilene Sue Ruhoy

Home Address:
2915 Montessouri Street
Las Vegas, NV 89117

Degrees:
Bachelor of Science, Biology, 1996
Marymount College

Doctor of Medicine, 2000
University of Pittsburgh School of Medicine

Publications:


Daughton CG and Ruhoy IS “PharmEcovigilance: Aligning Pharmacovigilance with Environmental Protection,” In: An Introduction to Environmental Pharmacology


Posters:

Dissertation Title: Examining Unused Pharmaceuticals in the Environment

Dissertation Committee:
Chairperson, Dr. David M. Hassenzahl, Ph.D.
Committee Member, Dr. Christian G. Daughton, Ph.D.
Committee Member, Dr. Shawn Gerstenberger, Ph.D.
Committee Member, Dr. Christopher Williamson, Ph.D.
Graduate Faculty Representative, Dr. Larry Ashely, Ed.S.