Beyond the Medicine Cabinet:
An Analysis of Where and Why Medications Accumulate

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Abstract

Active pharmaceutical ingredients (APIs) from medications can enter the environment as trace contaminants, at individual concentrations generally below a part per billion (µg/L). 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.

APIs also enter the environment from the disposal of unwanted medications directly to sewers and trash. 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.

This paper 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 drugs 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.

Keywords: Pharmaceuticals; Medications; APIs; Accumulation; Disposal; Environmental pollution; Pollution prevention

Introduction

Pharmaceuticals have myriads of uses for both humans and animals, including 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 levels 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 in the first place 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 paper 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. This paper presents the first

comprehensive examination of why 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. This paper also presents a summary of the first comprehensive cataloging of the types and quantities of APIs disposed by a defined subpopulation into known sewage treatment plants; these first-ever data provide insights regarding what classes of drugs most commonly accumulate and require eventual 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. We had previously presented a new 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 as outlined by Ruhoy and Daughton (2007).

Another aspect of drug disposal 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).

Accumulated, leftover medications pose several major problems with respect to both human health and safety and the integrity of the environment. These problems result from the diversion of accumulated drugs to those for whom they were not intended (leading to accidental or purposeful poisonings of infants, children, adults, and pets) and from the disposal of accumulated drugs to trash and sewage, from where the APIs can then enter the ambient environment, posing risk of exposures for wildlife or eventually for humans via drinking water supplies or food (Daughton, 2007, 2008; Ruhoy and Daughton, 2007).

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 U.S. 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

In this paper, we ask whether the disposal of drugs could be controlled by implementing any number of pollution prevention or stewardship measures. 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). 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 U.S., 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 U.S., 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 U.S. 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 landfilling 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-adherence (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 (see 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 U.S. 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 many of the locations where drug buildup and eventual disposal could occur is presented in Figure 1. 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.

This paper presents a descriptive narrative for the flow chart. 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. 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 paper, see Velagaleti and Burns (2007).

The following discussion is organized in two Tables (1 & 2) that describe and evaluate: (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. These are summarized in Tables 1 and 4. 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 2 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.

Table 1. Factors Leading to the Generation of Leftover, Unwanted Medications

Promotionals

York University (2008) researchers estimate the U.S. 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 (U.S. 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 (programs that attempt to counter-balance promotionals)

Counter-promotion involves programs and interventions to teach health professionals or students to critically assess drug promotion - - 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 U.S., 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 (inhalation), 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) is now available (as one example, see Parata Systems: http://www.parata.com/adhere/index.php).

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). 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 paper uses the words synonymously since the end-result is very similar.

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 U.S. 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 a physician may believe they have explained the disease and the relevant physiology of the disease and drug's mode of action, in reality, the 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.

Table 2. 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) requires 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, it 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.

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 U.S. are not available. In 1999, drug companies gave doctors free medications worth more than U.S. $7.2B (billion: one thousand million) 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 U.S. $57.5B, or roughly $61,000 per physician. 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 (U.S. 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) has revealed the presence of unused sample packages with almost 5% of the decedents (unpublished).

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 U.S. EPA Office of Water 2008 Effluent Guidelines Program (U.S. 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 (U.S. 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 (U.S. 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 (U.S. 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 (see Figure 2) includes behaviors such as forgetting to take the medication, deliberate under-dosing, and hoarding medications to take later. 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, there is one new source of data that can lend some insight as to the types and quantities that occur. This source is coroner inventory data - - first described and discussed by 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 U.S. These take-backs are becoming 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 U.S., 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.

The 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-inflammatories, 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 U.S. 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 U.S. 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.dmsbfda.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 U.S. (Ruhoy and Daughton, 2007). They also represent a previously unrecognized source of disposal themselves. We have 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, for the first time, calculations of influent concentrations (averaged over time) for STPs. A detailed exposition of the data collected to date will be published (Ruhoy and Daughton, in preparation). In Table 3, however, we present 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.

Discussion

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 — but 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 our proposal to use coroner inventory data to begin collecting real-world disposal data from known segments of the population (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 "The Afterlife of Drugs and the Role of PharmEcovigilance," Environmental Health Perspectives, submitted 2008). These spikes in concentrations could lead to increased exposure for aquatic organisms, for example, should the APIs survive sewage treatment; 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 (see Table 5). These aspects serve as additional imperatives for ensuring that the disposal of drugs is environmentally sound.

From our evaluation and analysis of the many aspects of drug accumulation and storage, it is clear that the factors controlling drug wastage and leading to disposal are numerous, varied, widespread, and complex. Although our 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 we term 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 <u>sustained</u> 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, we recommend 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; our summary data presented in Table 3 provides an example.

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, Antiinfectives, and Musculo-Skeletal System (Table 3). 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 from playing roles with respect to overall hazard in the aquatic environment.

The major opportunities for pollution prevention are summarized in Table 4. 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 prescriptions 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 is an oft-cited 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 U.S. 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 and dental 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 1 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.

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Table 3. Summary of API Masses Disposed to Sewerage by a Coroner Office during a 12-Month Period[†]: Categorized by Therapeutic Class[‡]

ATC Code	ATC Main Group	Quantity (mg) disposed	#of APIs	% of Total
A	Alimentary Tract	18,685,271	56	34.6
N	Nervous System	16,510,963	95	30.6
C	Cardiovascular System	6,331,976	71	11.7
J	Antiinfectives	5,608,735	45	10.4
M	Musculo-Skeletal System	3,851,949	21	7.1
R	Respiratory System	984,780	16	1.8
B	Blood	721,450	9	1.3
V	Various	622,800	1	1.2
P	Antiparasitics	236,269	2	0.44
L	Antineoplastics	186,013	14	0.34
G	GU System & Sex Hormones	146,440	23	0.27
H	Hormonal Preparations	50,601	10	0.09
S	Sensory Organs	4,375	1	0.008
D	Dermatologicals	3,420	3	0.006
	TOTAL	53,945,042	367	

[†] 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 large 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 U.S. 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 4. Major Opportunities for Preventing the Wastage and Accumulation of Medications	
Unit dosing	Unit dose (and unit-of-use) dispensing absolutely 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), is at best marginal (Larsen and Haugbølle 2007) but still equivocal (Connor et al. 2004); this is an important area for further investigation. 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: http://www.parata.com/adhere/index.php
Trial scripts	Allow for management of ineffective treatment, adverse effects, or poor compliance. Necessary before prescribing multi-month supplies.
Low-quantity packaging of OTC medications	Lessens chance of expiration. Allows consumer to experiment before deciding whether a larger quantity is warranted.
Increased monitoring of patient	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.
Implement practice of concordance	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 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).
Free samples & Donations	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 is covered by McKee (2006). Various state legislation pertinent to drug reuse has been proposed or passed since 2006 (NCSL 2008).
Reduce incentives for excessive purchasing	Implement procedures that would encourage insurance companies and pharmacies to re-evaluate procedures for dispensing large quantities of medication that later are never used. Better control automatic refills, especially for the deceased.

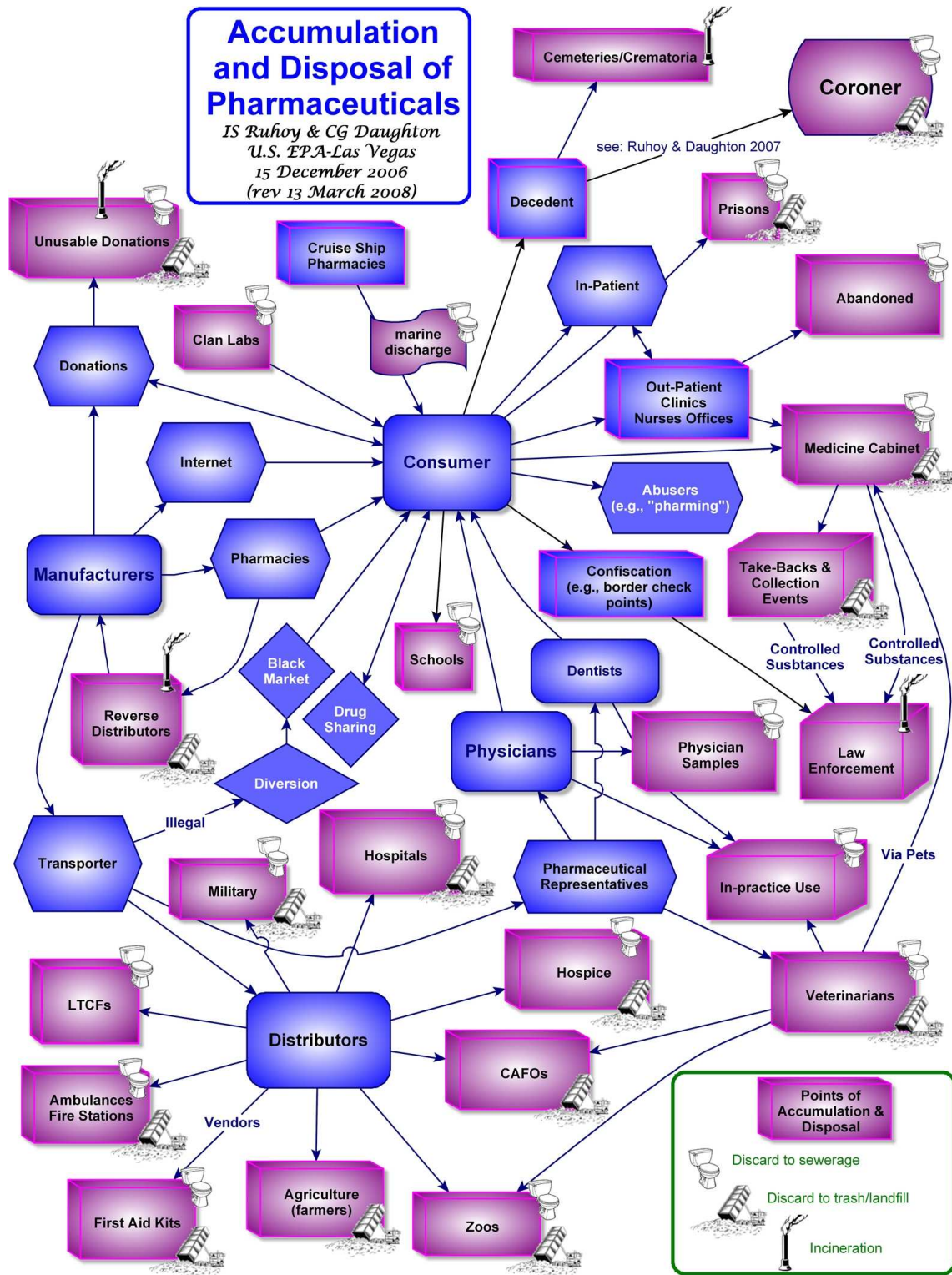| **Table 5.** Unique Aspects of Drug Disposal via Flushing (in Contrast with Excretion/Bathing) that Could Prove Environmentally Significant	
Episodic release	Release by disposal from just one or a few individuals might result in brief, episodic, transient spikes in concentrations of APIs in sewage - - 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).
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.
Location of disposal	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.

Figure 1. Accumulation and Disposal of Pharmaceuticals

Figure 2. Factors Influencing Drug Consumption

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