

Drug Usage and Disposal: Overview of Environmental Stewardship and Pollution Prevention (with an emphasis on some activities in the Federal Government)

prepared by: Christian G. Daughton (daughton.christian@epa.gov), US EPA, Office of Research and Development, Environmental Sciences Division, Las Vegas, Nevada

prepared for: Research Triangle Environmental Health Collaborative - Health Summit, 10-11 November 2008, North Carolina Biotechnology Center, Research Triangle Park, North Carolina

Introduction

This article provides the background for understanding the many complex variables that combine to cause pollution of the environment with the active ingredients from pharmaceuticals. It also summarizes the many approaches that could potentially reduce this pollution. Significantly, actions designed for pollution prevention or pollution reduction hold the potential to also reduce healthcare expenses, improve therapeutic outcomes, and moderate the long-persisting national problem of morbidity and mortality caused by poisonings of infants, children, adults, pets, and sometimes wildlife. These collateral benefits are important to this discussion because one of the major unknowns regarding the various pollution control actions (such as reducing generation and disposal of unwanted drugs) is whether they would actually result in significantly reduced pollution. The main driving force for reducing pollution may have more to do with human health and safety.

Over the last decade, a new dimension to environmental pollution has become evident - one involving the actions, behaviors, and activities of the individual consumer as a source of chemical pollutants. A major focus on consumer-use chemicals has been directed at the numerous types of chemicals formulated into thousands of different pharmaceutical products. The ubiquitous worldwide use of pharmaceuticals has led to the first realization that the seemingly insignificant contributions from multitudes of individuals can combine to result in measurable levels of newly recognized pollutants in the environment . These countless, individual point sources result in environmental loadings of a wide spectrum of chemicals, most of which are designed to have biochemical activity at relatively low concentrations, all with largely unknown potential for adverse impacts on non-target organisms. This new dimension to understanding chemical pollution is unique in that many of the chemicals involved are widely viewed as being desirable or beneficial, and sometimes essential, to the health, well-being, and sometimes survival of humans and domestic animals.

The active ingredients from medications and other pharmaceutical preparations can pose risks beyond those associated with their intended uses in therapy, diagnosis, or prophylaxis. These “unintended” risks comprise two major categories: (1) introduction to the environment as trace

pollutants by the combined actions and activities of individuals, resulting in chronic low-level exposure for wildlife and humans (e.g., via recycling in drinking water), and (2) their involvement in exposure to wildlife and humans at acute doses, primarily from special situations involving imprudent disposal and from accidental or purposeful ingestion by individuals for whom the medications were never intended (i.e., drug diversion).

Each of these two major categories comprises several sources or origins. Active pharmaceutical ingredients (APIs) enter the environment by way of: (1) the excretion of unmetabolized API (as well as bioactive metabolites), (2) release from the skin during bathing (from medications applied dermally and from residues excreted through the skin via sweat) [Daughton and Ruhoy 2008 submitted], (3) disposal to sewerage or trash of unwanted, unused, leftover medications, and (4) animal carcasses containing high levels of certain drugs (these tainted carcasses can contain levels of certain APIs that are acutely toxic to animal scavengers [Daughton 2007]). The many pathways by which drugs and their APIs are distributed into the environment and by which they can eventually come into contact with wildlife or result in unexpected, unintended exposures for humans are summarized in Figures 1 and 2. A number of parallels exist regarding these sources with respect to the use of human pharmaceuticals and veterinary pharmaceuticals (especially with regard to confined animal feeding operations, CAFOs); for CAFOs, however, the classes of APIs are primarily limited to steroids, antibiotics, and anti-inflammatories.

This overview focuses primarily on the third origin (i.e., disposal) and the actions and activities surrounding environmental stewardship involved with reducing the contributions of APIs to the environment from this source, via pollution prevention and source control. The overview summarizes the many questions and unknowns regarding drug disposal. Its focus is on the disposal of leftover drugs from the consumer sector rather than the healthcare community and other commercial medical establishments (e.g., hospitals, long-term care facilities, hospices, diagnostics clinics, etc). The laws and regulations in the U.S. pertaining to the consumer sector often differ from those for the healthcare communities (especially with regard to RCRA). Of key significance is the restrictions imposed on disposal alternatives by the Controlled Substances Act, as administered by the Drug Enforcement Administration [Daughton 2007]. It cannot be overemphasized that the issues surrounding drug disposal are remarkably complex. Many of the solutions that have been implemented by other countries for several decades have not been feasible in the U.S.

Long overlooked in the debate surrounding drug disposal is the larger imperative to reduce or eliminate the need for disposal in the first place - - by a wide spectrum of approaches targeted at pollution prevention. Drugs accumulate unused for a wide variety of reasons, each of which presents opportunities for reducing the need for disposal [Ruhoy and Daughton 2008]. These reasons, which range from patient non-compliance (which itself has a plethora of causes), inefficient oversight of the prescribing process by physicians, imprudent dispensing practices by the retail pharmacy and insurance industry, and wasteful packaging by manufacturers. A wide array of causes for accumulation and subsequent disposal are summarized by Ruhoy and Daughton [2008]; many of these are summarized in Figure 3. Another significant aspect of medication accumulation is the broad spectrum of locations in society where medications are stored and where they eventually can accumulate unused (for example, upon expiration), ranging

from zoos and all public buildings (e.g., first aid kits), to schools and cruise ships; many of these are summarized in Figure 4. The numbers and types of places go far beyond the traditional view of the home medicine cabinet.

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

With this said, however, the focus in the U.S. has remained on how to best dispose of drugs using ecologically sound disposal practices, rather than on the need to generate less medication waste. To date, this has been done with relatively inefficient one-time community collection events or in-place local programs that vary in their scope and design across geographic locales. These consumer-based collection approaches are also known as "take-backs" or "returns." A disparate patchwork of collection programs exist sporadically across the U.S. The EPA is currently evaluating a pilot demonstration of one approach that may prove to be more sustainable - - and one that could be implemented nationwide - - designed to make use of the US Postal Service [Gressitt 2005; Univ. Maine 2008]. A second pilot program involves the return of consumer medications through a pharmaceutical reverse distributor via UPS [Genco 2008]. While consumer take-back programs are a relatively new concept in the U.S., they have been in place in Europe for over 30 years. Two of the earliest publications dealing with take-backs are:

Bradley TJ and Williams WH (1975). Evaluation of medicines returned in Manchester DUMP campaign. *Pharm J* 215:542.

Harris DW, Karandikar DS, Spencer MG, Leach RH, Bower AC and Mander GA (1979). Returned-medicines campaign in Birmingham. *Lancet* 313(8116):599-601.

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

PharmEcovigilance would merge traditional pharmacovigilance with ecopharmacovigilance - - encompassing the many dimensions of both ecological and human health. It would emphasize that human and ecological health are intimately connected. It would seek to optimize the design of the life cycle of drug manufacturing, sales/distribution, and usage by ensuring: (1) prescribing

the most effective medications in efficacious minimal doses individualized for each patient, (2) dispensing in quantities and for durations that ensure patient compliance (full consumption), and (3) minimizing/eliminating the generation of leftover medications — so the need for disposal is avoided. Its major objectives would be to: (1) minimize impacts on the environment from APIs as pollutants, (2) minimize exposure of humans via consumption of APIs "recycled" from the environment (trace residues in drinking waters and foods), and (3) minimize hazards posed to safety and health from diversion or scavenging of unused medications by humans, pets, and wildlife [Daughton 2008; Daughton and Ruhoy 2008a].

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

The many actions that could be considered for prudently reducing drug use (and thereby reduce the need for disposal) have been summarized in several publications: Daughton 2003a,b, Daughton and Ruhoy 2008a, and Ruhoy and Daughton 2008. The prudent reduction in overall medication usage could minimize the need for disposal. **To reiterate, in contrast to improving the drug disposal process, pollution prevention actions might all afford the potential for significant collateral benefits in reducing healthcare costs and improving therapeutic outcomes, as well as reducing entry of APIs to the environment via excretion and bathing.** The major emphasis to date, however, has been on improving approaches for drug disposal. The most important thing to keep in mind with respect to disposal is the many unknowns regarding its benefits and sustainability. These unknowns will serve as the focus of much of the discussion that follows.

Significant Past and Present Activities Sponsored by the Federal Government Regarding Drug Disposal

Various agencies within the U.S. federal government have been involved with a number of actions and activities focused on some of the issues surrounding drug disposal. The major ones are summarized here:

The **Institute of Medicine** (IOM), National Academy of Sciences, held two workshops on emerging pollutants, with a focus on pharmaceuticals, both hosted by the Roundtable on Environmental Health Sciences, Research, and Medicine (EHSRT), Washington, DC. The first (“Human Health Effects of Using Antimicrobial Agents in Agriculture”) was on 9 December 2002, and the second (“Source Water to Drinking Water: Emerging Challenges for Public Health) was held on 16 October 2003.

The first national conference on drug disposal was held by the **US EPA**: "U.S. EPA Workshop on Pharmaceuticals in the Environment," Office of Research and Development, National Exposure Research Laboratory, Las Vegas, NV, 23-25 August 2005.

The **Drug Enforcement Administration** (DEA) held the first public meeting directed at drug disposal, with emphasis on the role of the Controlled Substances Act (CSA): "End User Drug Disposal Conference," organized by the DEA, Seattle Field Division, Portland District Office, Portland, OR, 25-26 April 2006.

The **EPA's Office of Water** is developing their Health Sector Information Collection Request (ICR), which will be used in a detailed study of unused pharmaceutical disposal methods by hospitals, long-term care facilities, hospices, and veterinary hospitals. As part of the annual review of Effluent Guidelines (<http://www.epa.gov/guide/304m/>), the ICR will enable creation of best management practices for disposal of unwanted and unused pharmaceuticals in the healthcare sector, thereby reducing the quantities of drugs entering in the influent to POTWs. An interim report was issued in August 2008:
<http://www.epa.gov/guide/304m/2008/hsi-tech-study-200809.pdf>.

The **US EPA's OCHP (Office of Children's Health Protection)** developed the nation's first extramural grants program involving the disposal of unwanted, leftover drugs (beginning in 2006: http://www.epa.gov/aging/grants/grant-list/2006_0804_solicitation-06b-8.pdf). Two grants were awarded for pilot projects:

Area Resources for Community and Human Services (ARCHS)

<http://www.epa.gov/aging/grants/winners/archs.htm>

University of Maine Center on Aging

<http://www.epa.gov/aging/grants/winners/umca.htm>

The **US EPA's Office of Solid Waste** is proposing to incorporate pharmaceuticals into the federal Universal Waste Rule. The proposed rulemaking is due to be published in December 2008, when it will become available for comment and revision. This rule is intended to facilitate creation of drug collection programs and limit their disposal to sewage. The rule lists pharmaceuticals as "universal waste," and will help overcome complications and costs associated with RCRA hazardous waste regulations. RCRA subjects many chemicals found in pharmaceuticals to hazardous waste rules, which set strict waste handling, record-keeping, and personnel training requirements, and also necessitates incineration. See:

<http://yosemite1.epa.gov/opei/Smallbus.nsf/04b7c5966aaff142852570150047179e/273617ce3ab52bbb852572ec006af28c!OpenDocument>

It is important to note, however, that only about 5% of drugs in the marketplace would be impacted by inclusion into the Universal Waste Rule because universal waste is a subset of RCRA hazardous waste. Treatment at a RCRA-permitted hazardous waste incinerator would still be required for that 5%, and the remaining 95% would remain unregulated federally.

The **US EPA Regional PPCPs Network** was formed in March 2007. Coordinated by Regions 3 & 5, this is the primary communications network for the Regions. After early leadership from Region 9, a wide array of local, regional, and state-wide programs and events have been

organized over the last couple of years as interim solutions to promoting public awareness of the need for proper drug disposal; see summary at: Illinois-Indiana Sea Grant [2008].

The **White House Office of National Drug Control Policy** (ONDCP), in collaboration with the EPA and FDA, implemented the nation's first public guidance on consumer drug disposal (issued in February 2007): "Proper Disposal of Prescription Drugs" (http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html).

U.S. Fish and Wildlife Service (in partnership with the American Pharmacists Association and the Pharmaceutical Research and Manufacturers of America) implemented a public awareness campaign in 2007 on consumer drug disposal, patterned largely from the ONDCP guidance: "SMARxT Disposal" (<http://www.smarxtdisposal.net/>).

Under the auspices of the **White House National Science and Technology Council** (under the Office of Science & Technology Policy), the first Federal Interagency Task Group on Pharmaceuticals in the Environment (PiE) was created in September 2004, under the Council's Subcommittee on Health and the Environment (then Toxics and Risks). The PiE Interagency task Group is jointly chaired by the U.S. FDA (Dr. Suzie Fitzpatrick), USGS (Herb Buxton), and EPA (Dr. Hal Zenick). One of the many areas of investigation of the Task Group is environmental stewardship.

Congress. Under the **Senate Environment and Public Works Committee** on Pharmaceuticals in Water (15 April 2008), the Senate Subcommittee on Transportation Safety, Infrastructure Security, and Water Quality held the hearing "Pharmaceuticals in the Nation's Water: Assessing Potential Risks and Actions to Address the Issue." The hearing was broadcast live; the video (ca. 1':50") of the verbal testimony and questioning can be accessed here: http://epw.senate.gov/public/index.cfm?FuseAction=Hearings.Hearing&Hearing_ID=30641a14-802a-23ad-4b51-a10dd439793f

EPA's Office of Research and Development has published a core group of articles in the peer-reviewed literature that address the many facets of pollution prevention, environmental stewardship, and sources/routes of entry to the environment relevant to APIs. These include: Daughton [2002, 2003a,b, 2007, 2008], Daughton and Ruhoy [2008a, 2008 submitted], and Ruhoy and Daughton [2007, 2008].

The **US EPA** has created the first comprehensive, publically accessible listing of literature citations that are directly or peripherally relevant to the many aspects of PPCPs as environmental pollutants. The listing is currently available from the EPA's PPCPs web site: <http://www.epa.gov/ppcp/lit.html>. A more extensive and comprehensive version is available in-house to EPA researchers as a full database and is compiled using bibliographic citation software. This project compiles publications covering all the facets of the risk assessment paradigm (including: Origins, Sources, Occurrence, Transport, Fate, Exposure, Effects, Stewardship, Monitoring, Waste & Water Treatment Technologies, Risk Assessment, Risk Communication, etc.) as well as many aspects that are peripherally related (e.g., major citations dealing with low-dose effects, mixture effects, and databases for medications, physicochemical properties, and toxicology, among others). The scope of the covered literature includes not just

journal articles, but also books (and book chapters), proceedings, databases, web pages, reports, miscellaneous gray literature, and select presentations and news stories. Of significance regarding drug disposal, is that of the current 5,700+ citations, the database contains only 250 or so references that pertain to disposal. While this is the largest collection of drug disposal references ever assembled, it represents a very minor portion (less than 5%) of the total number of references available on all aspects of PPCPs as pollutants.

Significant Activities Sponsored by the Medical/Pharmacy Communities Regarding Drug Disposal

The following are some of the formal resolutions regarding drug wastes that have been adopted by medical and pharmacy service associations: (i) In 2006, the AMA House of Delegates drafted D-135.993 (Resolution 403) on "Contamination of Drinking Water by Pharmaceuticals and Personal Care Products," (ii) the American Society of Consultant Pharmacists (2003; where unused non-controlled substances dispensed by long-term care facility pharmacies may be returned to the pharmacy for reuse), (iii) the U.S. Pharmacopeia Convention (2005; to aim at working with "appropriate constituencies to continue developing programs to promote safe medication use and disposal"), (iv) Assembly of the American Psychiatric Association (May 2005; endorsed a paper encouraging state and federal legislation for programs aimed at the proper disposal of unused pharmaceuticals), (v) the National Association of Boards of Pharmacy (2006; adopted a resolution to "Develop Legal and Environmentally Safe Programs for the Disposal of Unwanted Medications"), and (vi) the American Society of Health-System Pharmacists (Policy Position #0611 "Redistribution of Unused Medications," and Policy Position #0614 "Safe Disposal of Patients' Home Medications," 2008; http://www.ashp.org/s_ashp/doc1c.asp?CID=512&DID=7300).

The following reference is a key resource on medication waste in the healthcare industry: Smith C et al. (August 2008). Managing Pharmaceutical Waste: A 10-Step Blueprint for Health Care Facilities In the United States. Healthcare Environmental Resource Center. 93 p. Available: http://www.practicegreenhealth.org/page_attachments/0000/0102/PharmWasteBlueprint.pdf

Some of the Key U.S. Organizations with Interest or Activities Directed at Pollution Prevention and Drug Disposal

AAPCC: American Association of Poison Control Centers (<http://www.aapcc.org/>). William Watson (watson@poison.org).

The Alliance: National Alliance for Model State Drug Laws (<http://www.natlalliance.org/>).

AMA: American Medical Association (<http://www.ama-assn.org/>).

APA: American Psychiatric Association (<http://www.psych.org/>).

APhA: American Pharmacists Association (<http://www.aphanet.org/>).

ASHP: American Society of Health-System Pharmacists (<http://www.ashp.org/>).

AVMA: American Veterinary Medical Association (prudent use of antimicrobials: http://www.avma.org/issues/jtua/jtua_swine.asp; <http://www.avma.org/scienact/jtua/default.asp>).

AWWA: America Water Works Association (<http://www.awwa.org/>).

CDC: NCIPC (National Center for Injury Prevention and Control: <http://www.cdc.gov/ncipc/default.htm>) and NCID (National Center for Infectious Diseases: <http://www.cdc.gov/drugresistance/>).

DEA: U.S. Drug Enforcement Administration (<http://www.usdoj.gov/dea/>): Ursula Bivens (L.Ursula.Bivens@usdoj.gov) and Deirdre McDonnell.

EPA: U.S. Environmental Protection Agency (<http://www.epa.gov/ppcp/>). Offices having active roles in drug disposal: Office of Research and Development (ORD), Office of Water (OW), Office of Solid Waste (OSW), Office of Children's Health Protection (OCHP), Office of Pollution Prevention and Toxics (OPPT).

FDA: U.S. Food and Drug Administration (<http://www.fda.gov>). Deborah Leiderman, leidermand@cderr.fda.gov, Director, Controlled Substance Staff, CDER.

IISG: Illinois-Indiana Sea Grant (<http://www.iisgcp.org/unwantedmeds/index.htm>).

Maine BSG: Maine Benzodiazepine Study Group (<http://www.mainebenzo.org/>).

MIRT: Medical Industry Waste Prevention Roundtable (<http://www.pprc.org/mirt/topics/pharmwaste.cfm>).

NABP: National Association of Boards of Pharmacy (<http://www.nabp.net/>).

NADDI: National Association of Drug Diversion Investigators (<http://www.naddi.org/>): Charlie Cichon, President (Eli Lilly and Company), ccichon@naddi.org.

NCPIE: National Council on Patient Information and Education (<http://www.talkaboutrx.org/index.jsp>).

NERC: Northeast Recycling Council (<http://www.nerc.org/>): Lynn Rubinstein, nerc@sover.net.

NIDA: National Institute on Drug Abuse (<http://www.nida.nih.gov/nidahome.html>): Dr. Nora D. Volkow, NIDA Director, volkow@bnl.gov.

ONDPCP: White House Office of National Drug Control Policy (http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html): Jennifer deVallance ([Jennifer L. deVallance@ondcp.eop.gov](mailto:Jennifer_L_deVallance@ondcp.eop.gov)).

PH:ARM: Pharmaceuticals from Households: A Return Mechanism (<http://www.medicinereturn.com/>).

PhRMA: Pharmaceutical Research and Manufacturers of America (<http://www.phrma.org/>).

PGH (aka Hospitals for a Healthy Environment): Practice Greenhealth (<http://www.practicegreenhealth.org/>).

PSI: Product Stewardship Institute (<http://www.productstewardship.us/displaycommon.cfm?an=1&subarticlenbr=181>).

USDA: NRCS (National Resources and Conservation Service) CAFO Rule and waste management (<http://www.nrcs.usda.gov/news/speeches04/caforuleimp.html>).

USFWS: "SMARxT Disposal" program (<http://www.smarxtdisposal.net>).

WateReuse Association: <http://www.watereuse.org/>.

WEF: Water Environment Federation (<http://www.wef.org/>).

Some Notable Needs Regarding Communication and Coordination

After a cursory examination of the published literature on stewardship, pollution prevention, and drug disposal, coupled with examination of the wide spectrum of organizations playing various role in these topics, it becomes obvious that an overarching framework might be useful in coordinating these disparate and overlapping activities. A coordinating framework could serve to better promulgate what is known, facilitate setting priorities, reduce discrepancies and contradictions, and reduce duplication of effort.

A lack of communication, interaction, and collaboration persists between the environmental sciences and the healthcare/medical communities on issues residing at the interface between the two. Those involved with studying the environmental aspects of drugs as pollutants, for example, generally operate in isolation from those involved with developing environmental stewardship programs. Bridging this gap could benefit both sides of the issue. Closer communication and collaboration could result in productive and efficient synergies.

The issues surrounding the disposition of drug wastes generated by consumers differ greatly from those for the healthcare industry. The two separate fronts may eventually need to be unified, at the least to promote discussion and collaboration among the separate stakeholders.

While the environmental science community and those involved with stewardship are aware of the issues surrounding drugs as pollutants, this is not necessarily true for those involved in the medical/healthcare communities, the dispensing community, and the healthcare insurance industry. Fostering recognition among those who prescribe, dispense, and insure will be essential for the developing high-impact approaches for pollution prevention. The most significant challenge will be to establish clear linkages between the health of the environment and human health [Daughton and Ruhoy 2008a].

No central public database exists that comprehensively compiles the numerous activities nationwide relevant to drug disposal (e.g., take back events and programs) and stewardship.

A major point of confusion, especially for scientists, is that projects and events that collect unused drugs from the public and that attempt to quantify their success often use widely different approaches for measuring and reporting the quantities of collected drugs. The most common shortcoming is that attempts at providing inventories of collected drugs often fail to report the units that are being measured. In order for comparisons to be possible between projects, or for scientists to use the data for predictive modeling purposes, it is essential that the units of measurement be defined. A range of approaches are used by these projects and often are not specified. The measures used include the mass of each API itself, the mass of the entire formulated medications themselves (e.g., tablets and capsules, including all excipients), the mass of the medications plus their consumer-use packaging, the mass of medications plus packaging and shipping containers, or the volume. These all will obviously yield wildly different values (which can vary over many orders of magnitude). But the only one that has relevance with regard to ecotoxicology and human health is the first: the mass of each individual API.

Would collected data be more useful if a standard approach were also used for cataloging and grouping APIs? One approach would be to use an international standard for categorizing the APIs according to their action on therapeutic systems, such as the Anatomical Therapeutic Chemical (ATC) Classification System. An example using this approach is presented in Ruhoy and Daughton [2008, Table 3].

Finally, a question that has been asked over the last 3 years is whether the Drug Enforcement Administration can be more effectively engaged in a dialog to rewrite the Controlled Substances Act (CSA) or provide the requisite waivers, in order to avoid the complications and hurdles the Act currently imposes on the design, scope, and efficiency of consumer drug take-back programs. An alternative would be for Congress to make this activity a priority and amend the CSA to enable safe, secure, and efficient take-back programs possible.

Some Notable Science Needs, Gaps, or Questions

Currently, over 5,700 documents have been published (largely in the scientific press) that are directly or peripherally related to the many aspects of drugs as pollutants. The citations for these publications are available here:

U.S. EPA. 2008. "Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature," U.S. Environmental Protection Agency, Las Vegas, NV; available: <http://www.epa.gov/ppcp/lit.html>.

Of these thousands of publications, roughly only 250 pertain to disposal (or stewardship); nearly half of these have been published since 2005. While this is the largest collection of references relevant to drug disposal ever assembled, it represents less than 5% of the total published on all other aspects of the topic. This shows in part that those who are involved with the drug disposal issue tend to not be publishing scientists. Drug disposal has not received the same degree of attention by scientists or engineers that any of the other aspects of the larger topic have, such as analytical chemistry, environmental monitoring, fate and transport, waste and water treatment, or effects on non-target organisms.

There are two basic approaches for reducing the entry of APIs to the environment. The first is environmentally sound practices for disposal of unwanted medications (disposal control). The second is the development of practices that reduce the prescribing and dispensing of medications by eliminating unnecessary or imprudent customs (usage control). Usage control is a very recent area of focus and therefore will require more attention. **Significantly, the control of usage is perhaps more capable of reducing overall entry of APIs to the environment, as it can eliminate the need for disposal plus minimize the residues released by excretion and bathing.** Usage control is much more complex than disposal control as it entails the involvement of the entire healthcare community, including healthcare insurers. This aspect was briefly mentioned in the background section, where pertinent references were provided.

Questions Involving Control of Disposal or Usage

The following are some of the major unanswered questions pertaining to drug disposal and which will require some methodological investigations. The scientific study of drug disposal and drug usage (consumption) is partly required to determine the importance of developing and implementing effective drug disposal or stewardship programs.

The major unknown is whether a holistic stewardship program aimed at environmentally sound disposal of unwanted drugs would yield a significant reduction in potential human and ecological exposure. What portion of APIs in the environment originate from disposal - - versus excretion and bathing? The relative contributions from these different routes might vary dramatically from drug to drug or from class to class (e.g., antibiotics, analgesics, hormones, controlled substances, etc). It also might vary according to the type of packaging (e.g., bulk containers versus blister packs). For which drugs (if any) occurring in the environment is direct disposal (or spillage, such as from domestic animals) to sewage a significant source? This is a key question, as pollution prevention would require far less investment of resources than would the R&D and engineering required for improved end-of-pipe control technologies (for both wastewater and drinking water). If all leftover medications were prudently collected rather than disposed to sewage or trash, would there be any measurable reduction in environmental residues? A generalized answer may not be possible, as it probably depends on each individual API.

In the absence of a sufficiently comprehensive understanding of the possible ramifications of drug disposal, how can priorities be determined for assigning resources for developing holistic stewardship programs?

Can drug disposal lead to transient spikes in concentrations of APIs in influents to sewage treatment plants (STPs) or septic systems? If so, how important are these intermittent or episodic, transient surges in concentrations? Normally, excretion and bathing (two routes that probably lead to constant low-level input to sewerage and consequently) establish a continual presence in the aquatic environment for many APIs (imparting "pseudo-persistence" for those whose short half-lives would ordinarily lead to rapid losses) [Daughton 2002]. For example, the intermittent discharge of large quantities of particular drugs via disposal could possibly generate spikes leading to concentrations sufficiently high to have adverse effects on microbiota in STPs. Although transient spikes in API concentrations at STPs have never been demonstrated in real-world conditions, could they perhaps explain some of the excursions in concentration values often seen during environmental monitoring; this is an often observed problem for discrete sampling (e.g., grab samples) versus time-weighted integrative sampling.

To what extent are leftover drugs that accumulate or that are stockpiled in households or trash - - awaiting disposal - - responsible for human morbidity and mortality from either diversion (purposeful usage by those for whom the medication was not intended: e.g., abuse, addiction, pharming) or accidental/unintended exposure (e.g., ingestion by a toddler or pet).

How statistically biased are the data collected from drug take-back events? Are the participants representative of the population at large? Would the collection data be representative of return

rates sustained over longer periods of time? Can the data be used to extrapolate across the broader population and over time? Do drug collection events select for those who are motivated to have stockpiled their unused drugs over long periods of time until they locate an opportunity for disposal? This phenomenon could result in a consumer returning relatively large quantities of drugs that had been accumulated or stockpiled over the course of many years and yet be misinterpreted as a quantity that would be returned on a periodic basis. This makes it very difficult for drug collection events to use acquired data to predict future return rates. Reliable data on leftover drugs has been completely lacking. The first study to present a comprehensive summary of accumulation/disposal data acquired from a well-defined sub-population of a single city over the span of a year was published in Ruhoy and Daughton [2008; see Table 3]. This study made use of the comprehensive and accurate data residing in coroner records, an approach pioneered by Ruhoy and Daughton [2007]. These data open the door for assessing a wide range of issues. As one example, by using coroner inventory data coupled with pharmacokinetic data for each API, calculations can be performed to assess the potential significance of disposal with respect to environmental loadings.

Environmental stewardship involves much more than simply the prudent disposal of leftover drugs. Environmental sustainability is an aspect of drug disposal that has rarely been considered. Life-cycle assessments in particular have been largely overlooked. Examples of factors to consider are the energy demands of drug collection activities (e.g., costs associated with transportation used by consumers to participate in collection events); environmental costs (e.g., delayed pollution associated with landfill burial; emission of pollutants from combustion of wastes in incinerators not properly engineered); and acute risks for humans, pets, and wildlife (e.g., poisonings associated with stockpiled medications awaiting disposal, with medications improperly disposed in trash, or resulting from the act of attempting to denature or disguise medications before disposal to trash) [Daughton and Ruhoy, 2008 submitted].

Drugs are historically one of the leading causes of poisonings each year. Until 2007, poison control centers had long advised against discarding to trash and had instead favored discarding to sewerage (since this had been the best way historically available for protecting human safety, for example from accidental poisonings of children, adults, and pets, as well as from purposeful ingestion by those for whom a medicine was not intended). As a consequence, the disposal guidance developed by the ONDCP [2007] and US FWS [2007] for consumers still recommends disposing of certain hazardous drugs (such as the antivirals entecavir, atazanavir, and stavudine, and the antibiotic gatifloxacin) or those likely to be diverted and abused, by flushing down the sewer. Is this list sufficiently comprehensive as to include all the medications that pose acute risks associated with diversion or poisonings if disposed to trash? Does this list contain drugs that could be better disposed to trash? The decision to flush or dispose to trash could also be based on whether flushing would make significant contributions of a particular API to the environment. This is a function of the pharmacokinetics of each API [Daughton and Ruhoy, submitted 2008]. For those APIs that are excreted largely unchanged, disposal of these drugs might contribute negligibly to environmental loadings. In contrast, for those APIs that are extensively metabolized, disposal could prove to be significant [Daughton and Ruhoy, submitted 2008]; also see Figure 5.

Another factor that has been little considered is the additional risk imposed by current disposal guidance. The ONDCP and US FWS (SMARxT) disposal guidance suggests the physical alteration of medications might be considered prior to placing in the trash. For certain medications, attempts to alter the medication or make it unpalatable poses risks to the consumer. For example, particulates from crushing can be inhaled, and whole pills or pieces can be spilled on floors where toddlers can reclaim them. Certain medications are specifically designed to resist mechanical alteration/destruction. Even removing or obliterating personal information on container labels from prescriptions can be much more difficult than imagined. Do these types of factors need to be re-evaluated in preparing the next generation of disposal guidance? Many of these factors have been discussed in detail for the first time by Daughton and Ruhoy [submitted 2008].

Do medications disposed to trash and then conveyed to landfills eventually pose a significant source of APIs in the leachates [e.g., see Musson and Townsend 2008]? Also, do drugs discarded to municipal landfills pose not just future environmental risks but also ongoing risks with regard to re-use by those who actively seek to reclaim them (e.g., human "gleaners" or animal scavengers)?

For guiding the responsible disposal of unwanted medications (a system protective of not just ecological integrity, but also human health), would an "environmental labeling" classification system be useful for the physician and consumer? One example is the program under development in a collaborative project between Sweden's Department of the Environment and the Stockholm County Council Pharmaceutical Unit [see: Daughton and Ruhoy, accepted 2008; Gunnarsson and Wennmalm 2008; Stockholm City Council 2008]. Labeling could provide advice on environmental disposition and possible environmental ramifications of improperly disposed materials. Likewise, labeling could possibly be used to guide the physician's selection of those medications having reduced environmental footprints.

Do the packaging materials (especially bottles and dispensers containing concentrated residuals) or the ever-increasing numbers of delivery devices once they have been used (e.g., delivery devices unique to certain drugs such as pumps, dermal patches, inhalers, syringes) pose a significant source of certain APIs? Do they constitute a significant source of non-API pollutants derived from the packaging itself (e.g., via incineration or weathering in landfills)? Could these problems be controlled by redesign of the packaging or by alternative disposal methods? Are the known extractables and leachables within dispensing devices and containers themselves a significant source of certain pollutants in the environment (e.g., plasticizers, nitrosamines, and acrylonitrile, deriving from plastics adhesives, antioxidants, coatings, vulcanizers, accelerants, adhesives)?

Many approaches are possible for extending the time to where medications require disposal because of expiry. Can "smart" or "intelligent" packaging systems, such as those used in the food industry, be adapted for medications - - with the objective of lengthening shelf life or monitoring and indicating the quality of the medication and whether it is reaching expiry? Examples include more effective oxygen and moisture scavengers and better ways for protecting against heat and light. Knowing the actual shelf life (which is a complex function of storage conditions and time)

could prevent the unnecessary, premature discarding of medications. The issues surrounding expiry are discussed by Daughton [2003a].

A recurring question has long surrounded the reuse, recycling, or sharing of unused medications so that others do not have to purchase new supplies. Medication recycling is fraught with dangers (such as tampering and self-medication errors). For this reason, it is usually only practiced where tight controls exist on the history of the medication. More information is in Daughton [2003b]. The question is whether safe programs can be developed for drug reuse or reintroduction into the distribution/retail chain.

Unknowns Regarding Usage Control

It is not possible to design a holistic stewardship program that protects both ecological and human health without an understanding of the complete life cycle of pharmaceuticals - - from the time of their discovery or design to their ultimate fate in the environment; see Figure 1. One obvious example is that entry of APIs into the environment cannot be prevented without a thorough understanding of the many contributing sources [e.g., Ruhoy and Daughton 2008]; see Figures 1 and 4. A less obvious example is the many factors that dictate whether a medication is ever actually used and how it is used, both of which are factors in whether it will require disposal [e.g., Ruhoy and Daughton 2008]. But complete lifecycle analysis has never been performed for any single API or class. The importance of lifecycle analysis has been discussed by Clark et al. [2007].

It is the combined events leading up to medications not being fully consumed that actually cause the need for disposal. These events include the vast and complex chain beginning with design/discovery, manufacturing, packaging, and advertising, and proceeding to prescribing (as modified by practices of healthcare insurers) and dispensing, and ending with whether the medications are eventually consumed or used by the consumer; see Figures 1-3. Many of the numerous aspects of these events have been covered in a number of papers, particularly Bound and Voulvoulis [2005], Clark et al [2007], Daughton [2003a,b; 2007], Daughton and Ruhoy [2008a, 2008 submitted], DeBolle et al. [2008], Doerr-MacEwen [2007], Ekedahl [2006], Kallaos et al. [2007], Langley et al. [2005], Mackridge and Marriott [2007], McKee [2006], Ruhoy and Daughton [2008], Seehusen and Edwards [2006], and Slack et al. [2005].

It is the numerous facets of the complex network of events contributing to the failure to fully consume medications that could be evaluated for the relative importance of their individual roles. Those that contribute the most to the generation of leftover medications, together with those contributors that could be easily and inexpensively rectified, could be targeted for actions to reduce their incidence or inefficiencies.

Finally, a significant point derives from the very fact that excess drugs accumulate and eventually require disposal. That leftover drugs exist points to pervasive problems in the ways in which drugs are marketed and distributed, how health care is administered, the fact that healthcare resources are being wasted, and to the very real possibilities that optimal therapeutic outcomes are not attained [Daughton and Ruhoy, 2008a; Ruhoy and Daughton 2008].

Core Listing of Selected References Relevant to Drug Disposal and Stewardship

The following references represent a core group that addresses the many facets of environmental stewardship, pollution prevention, and drug disposal; this core group comprises roughly 70 documents from the peer-reviewed literature, reports, web materials, and trade news stories. These references were selected from the larger group of roughly 260 that pertain to these facets and which had been extracted from the much larger EPA PPCPs literature database of broad scope (<http://www.epa.gov/ppcp/lit.html>). The subgroup of roughly 260 references represents the most comprehensive compilation of literature currently available on these aspects of PPCPs. Many of these references are extremely hard to locate and have therefore remained as obscure resources on environmental stewardship.

- Abahussain E and Ball D (2007). Disposal of unwanted medicines from households in Kuwait. *Pharmacy World Sci* 29(4), 368-373.
- Abahussain EA, Ball DE and Matowe WC (2006). Practice and opinion towards disposal of unused medication in Kuwait. *Med Princ Pract* 15(5), 352-357.
- Bay Area Pollution Prevention Group (2006). Report on the San Francisco Bay area's safe medicine disposal days. San Francisco, CA. 45 p. Available: <http://oracwa.org/files/news/168/SFBAYSafeMeds-Report-August2006.pdf>.
- Boehringer SK (2004). What's the best way to dispose of medications? *Pharmacist's Letter* 20(4), 200415.
- Bound JP, Kitsou K and Voulvoulis N (2006). Household disposal of pharmaceuticals and perception of risk to the environment. *Environ Toxicol Pharmacol* 21(3), 301-307.
- Bound JP and Voulvoulis N (2005). Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. *Environ Health Perspect* 113(12), 1705-1711.
- Bradley TJ and Williams WH (1975). Evaluation of medicines returned in Manchester DUMP campaign. *Pharm J* 215, 542.
- Braund R, Yuen YC and Jung J (2007). Identification and quantification of medication returned to Otago pharmacies. *New Zealand Family Physician* 34(4), 258-262.
- Clark J, Summerton L, Smith E, Kampa E, Vidaurre R and Touraud E (2007). Discussion Document on Eco-pharmacostewardship. KNAPPE: Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters. 59 p. Available: <http://www.knappe-eu.org/fichiers/47-D5.1%20Ecopharmacostewardship%20disc%20doc.pdf>.
- Coma A, Modamio P, Lastra CF, Bouvy ML and Marino EL (2007). Returned medicines in community pharmacies of Barcelona, Spain *Pharm World Sci* 30, 272-277.
- Daughton CG (2002). Environmental stewardship and drugs as pollutants. *The Lancet* 360(9339), 1035-1036. Available: <http://www.epa.gov/nerlesd1/bios/daughton/lancet-page.pdf>.
- Daughton CG (2003). Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. *Environ Health Perspect* 111(5), 757-774. Available: <http://www.epa.gov/nerlesd1/bios/daughton/green1.pdf>.
- Daughton CG (2003). Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions. *Environ Health Perspect* 111(5), 775-785. Available: <http://www.epa.gov/nerlesd1/bios/daughton/green2.pdf>.

- Daughton CG (2007). Pharmaceuticals in the environment: sources and their management. In: Petrovic M, Barcelo D, editors. *Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle*: Elsevier Science. p 1-58. Available: http://www.epa.gov/nerlesd1/bios/daughton/Chap1_Petrovic&Barcelo.pdf.
- Daughton CG (2008). Pharmaceuticals as environmental pollutants: the ramifications for human exposure. In: Heggenhougen K, Quah S, editors. *International Encyclopedia of Public Health*. Oxford: Academic Press. Vol. 5, p 66-102; <http://linkinghub.elsevier.com/retrieve/doi/10.1016/B978-012373960-5.00403-2>
- Daughton CG and Ruhoy IS (2008a). The Afterlife of Drugs and the Role of PharmEcovigilance. *Drug Safety* 31(12), 1-14.
- Daughton CG and Ruhoy IS (2008b in press). Accumulation and disposal of leftover medications: A key aspect of pharmEcovigilance. In: Rahman SZ, Gupta V, editors. *An Introduction to Environmental Pharmacology* Aligarh, India: Ibn Sina Academy.
- Daughton CG and Ruhoy IS (2008c in press). PharmEcovigilance: Aligning Pharmacovigilance with Environmental Protection. In: Rahman SZ, Gupta V, editors. *An Introduction to Environmental Pharmacology*. Aligarh, India: Ibn Sina Academy.
- Daughton CG and Ruhoy IS (accepted 2008). Pharmaceuticals and Sustainability: Concerns and Opportunities Regarding Human Health and the Environment,. In: Wennmalm Å, editor. *Sustainable Flow of Pharmaceuticals: Apoteket AB and Stockholm County Council in collaboration with the Research Project MistraPharma*.
- Daughton CG and Ruhoy IS (submitted 2008). Environmental Footprint of Pharmaceuticals - The Significance of Factors Beyond Direct Excretion to Sewers.
- De Bolle L, Mehuys E, Adriaens E, Remon J-P, Bortel LV and Christianens T (2008). Home medication cabinets and self-medication: A source of potential health threats? *Ann Pharmacother* 42, 572-579.
- DEA (2008). *General Questions & Answers: Can an individual return their controlled substance prescription medication to a pharmacy?* Washington, DC: Office of Diversion Control, Drug Enforcement Administration, US Department of Justice. Available: http://www.deadiversion.usdoj.gov/faq/general.htm#pre_med.
- Doerr-MacEwen NA (2007). *The Management of Human Pharmaceuticals in the Environment*. Doctoral Dissertation. Waterloo, Ontario: University of Waterloo. 267 p. Available: <http://uwspace.uwaterloo.ca/bitstream/10012/2751/1/Nora%20PhD%20thesis.pdf>.
- Doerr-MacEwen NA and Haight ME (2006). Expert Stakeholders' Views on the Management of Human Pharmaceuticals in the Environment. *Environ Management* 38(5), 853–866.
- Ekedahl A (2006). Reasons why medicines are returned to Swedish pharmacies unused. *Pharm World Sci* 28(6), 352-358.
- Fasola G, Aita M, Marini L, Follador A, Tosolini M, Mattioni L, Mansutti M, Piga A, Brusaferrero S and Aprile G (2008). Drug waste minimisation and cost-containment in Medical Oncology: two-year results of a feasibility study. *BMC Health Serv Res* 8(1), 70.
- Genco (2008). Pioneering Safe Medication Return Initiative Reviewed During Pharmaceutical Disposal Summit. Press Release, GENCO Supply Chain Solutions, 17 September 2008. Available: <http://www.pressreleasepoint.com/node/58419/pdf>.
- Götz K and Florian K (2007). Drug disposal in private households: Does the disposal of pharmaceuticals via domestic sanitary devices contribute to water contamination? [Medikamentenentsorgung in privaten Haushalten: Ein Faktor bei der Gewässerbelastung mit Arzneimittelwirkstoffen?]. *Umweltwissenschaften und Schadstoff-Forschung* 19(3), 180-188.

- Gressitt S (2005). Maine: First US Legislation for Unused Pharmaceutical Returns. U.S. EPA Workshop: Pharmaceuticals in the Environment, Office of Research and Development, National Exposure Research Laboratory Las Vegas, NV. 36 p. Available: http://es.epa.gov/ncer/publications/workshop/8-23-2005/Gressitt_0915_d3.pdf.
- Gunnarsson B and Wennmalm A (2008). Drug Design Should Involve Consideration of Environmental Risk and Hazard Lett in Drug Design & Discovery 5(4), 232-235.
- Halasi S (2005). Waste not, want not: a guide to appropriate disposal of used, expired or unwanted drugs. Pharmacy Practice (Canada: pharmacyconnects.com) 21(10), 34-41.
- Halford B (2008). Side Effects: Pharmaceuticals have been finding their way into our environment for a long time, but just what are they doing there? Chem Eng News 86(8), 13-17.
- Harris DW, Karandikar DS, Spencer MG, Leach RH, Bower AC and Mander GA (1979). Returned-medicines campaign in Birmingham. Lancet 313(8116), 599-601.
- Herring ME, Shah SK, Shah SK and Gupta AK (2008). Current Regulations and Modest Proposals Regarding Disposal of Unused Opioids and Other Controlled Substances. J Am Osteopath Assoc 108(7), 338-343.
- Hubbard ML (2007). Analysis of the Oregon Stakeholder Drug Take Back Public Policy Process to Reduce Pharmaceutical Pollution in Oregon's Water Resources. Masters Dissertation. Corvallis, OR: Oregon State University. 64 p. Available: <http://hdl.handle.net/1957/6192>.
- Illinois-Indiana Sea Grant (2008). Habitats and Ecosystems, Disposal of Unwanted Medicines: A Resource for Action in Your Community, unwantedmeds/updated Toolkit Materials. Available: <http://www.iisgcp.org/unwantedmeds/>.
- Kallaos J, Wheeler K, Wong C and Zahller M (2007). Pharmaceuticals in Wastewater Streams: Disposal Practices and Policy Options in Santa Barbara. Santa Barbara, CA: Donald Bren School of Environmental Science & Management. 129 p. Available: <http://www.bren.ucsb.edu/research/documents/PharmaceuticalsFinalReport.pdf>.
- Kuehn BM (2008). Traces of drugs found in drinking water: Health effects unknown, safer disposal urged. J Am Med Assoc 299(17), 2011-2013.
- Kummerer K and Velo G (2006). Ecopharmacology: A New Topic of Importance in Pharmacovigilance. Drug Safety 29(5), 371-373.
- Kuspis DA and Krenzelok EP (1996). What happens to expired medications? A survey of community medication disposal. Vet Hum Toxicol 38(1), 48-9.
- Langley C, Marriott J, Mackridge A and Daniszewski R (2005). An Analysis of Returned Medicines in Primary Care. Pharm World Sci 27(4), 296-299.
- Lynch JC and McCullough T (2008). The Collection and Disposal of Waste Medications. US Pharm 33(6), HS-20-HS-24.
- Mackridge AJ and Marriott JF (2007). Returned medicines: waste or a wasted opportunity? J Public Health (Oxford England) 29(3), 258-262.
- Marsalek J (2008). Pharmaceuticals And Personal Care Products (Ppcp) In Canadian Urban Waters: A Management Perspective. In: Hlavinek P, Bonacci O, Marsalek J, Mahrikova I, editors. Dangerous Pollutants (Xenobiotics) in Urban Water Cycle: Springer Netherlands. p 117-130.
- Martin SJL, Bilotas K, Cameron J, Carr DS, Earle WM, Gressitt S, Ketterer SP, McKinney R, Patterson S-L, Pistell A and others (2005). Final report of the Maine Drug Return Implementation Group. State of Maine 121st Legislature 34 p. Available: <http://www.maine.gov/legis/opla/drugrpt.pdf>.
- McKee G (2006). Keeping drugs out of the toilet: The need for federal action to allow consumer drug donation. Quinnipiac Health Law Journal 10(1), 45-76.
- Morgan TM (2001). The economic impact of wasted prescription medication in an outpatient population of older adults. J Fam Pract 50(9), 779-781.
- Musson SE, Townsend T, Seaburg K and Mousa J (2007). A continuous collection system for household pharmaceutical wastes: a pilot project. J Air Waste Mangement Assoc 57(7), 828-835.

- Musson SE and Townsend TG (2008 in press). Pharmaceutical compound content of municipal solid waste. *J Haz Mat* doi:10.1016/j.jhazmat.2008.05.089
- Paone RP, Vogenberg FR, Caporello E, Rutkowski J, Parent R and Fachetti F (1996). Medication Destruction and Waste Measurement and Management in Long-term Care Facilities. *Consult Pharm* 11, 32-40.
- PH:ARM (2007). Disposal of medications from residential consumers - Issues, barriers, and opportunities. Washington State. Team PffHARMP. 35 p. Available: <http://www.govlink.org/hazwaste/publications/Unwanted%20Medications%20Primer12-14-07.pdf>.
- Pharmacist's Letter/Prescriber's Letter (2007). Proper disposal of expired or unwanted drugs. *Pharmacist's Letter/Prescriber's Letter* 23(4), 230401.
- Pomerantz JM (2004). Recycling expensive medication: why not? *MedGenMed* 6(2), 4.
- Richman C and Castensson S (2008). Impact of waste pharmaceuticals: an environmental hazard or "greenwash"? *Pharm J* 280, 335-342.
- Rubinstein L (2006). Operating Unwanted Medication Collections - A Legal & Safe Approach. NERC Northeast Recycling Council Inc. 65 p. Available: www.nerc.org.
- Ruhoy IS and Daughton CG. 2007. Disposal as a Source of Pharmaceuticals in the Environment [Poster Presentation]. Las Vegas, NV: USEPA, NERL. Available: <http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-1.pdf>.
- Ruhoy IS and Daughton CG. 2007. Pharmaceutical Disposal and the Environment [Poster Presentation]. Las Vegas, NV: USEPA, NERL. Available: <http://www.epa.gov/nerlesd1/chemistry/images/drug-disposal-2.pdf>.
- Ruhoy IS and Daughton CG (2007). Types and quantities of leftover drugs entering the environment via disposal to sewage -- Revealed by coroner records. *Sci Total Environ* 388(1-3), 137-148. Available: <http://www.epa.gov/nerlesd1/bios/daughton/SOTE2007.pdf>.
- Ruhoy IS and Daughton CG (2008). Beyond the medicine cabinet: An analysis of where and why medications accumulate. *Environ Internat* 34(8), 1157-1169; doi:10.1016/j.envint.2008.05.002.
- Seehusen DA and Edwards J (2006). Patient Practices and Beliefs Concerning Disposal of Medications. *J Am Board Fam Med* 19(6), 542-547.
- Slack RJ, Zerva P, Gronow JR and Voulvoulis N (2005). Assessing quantities and disposal routes for household hazardous products in the United Kingdom. *Environ Sci Technol* 39(6), 1912-1919.
- Smith C (2008). Managing Pharmaceutical Waste: A 10-Step Blueprint for Health Care Facilities In the United States. Practice Greenhealth. 93 p. Available: http://www.practicegreenhealth.org/page_attachments/0000/0102/PharmWasteBlueprint.pdf.
- Smith CA (2003). The right prescription. Managing pharmaceutical waste is environmentally correct and the law. *Health Facil Manage* 16(5), 30-4.
- State of Maine (2005). An Act To Encourage the Proper Disposal of Unused Pharmaceuticals. Office of the Revisor of Statutes, Public Laws of Maine: Second Special Session of the 121st. Available: <http://janus.state.me.us/legis/ros/lom/LOM121st/15Pub651-700/Pub651-700-126.htm>.
- Stockholm City Council (2008). Environmentally Classified Pharmaceuticals. Stockholm, Sweden. Council SC. 32 p. Available: http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=10205.
- Subratty AH and Nathire MEH (2005). A survey on home generated medical waste in Mauritius. *Internat J Environ Health Res* 15(1), 45-52.
- TDC Environmental LLC (2004). Household pharmaceutical waste: Regulatory and management issues. San Mateo, CA: Prepared for the San Francisco Department of the Environment. 24 p. Available: <http://www.tdcenvironmental.com/HouseholdPharmWasteMgtIssuesFinal.pdf>.
- University of Maine (2008). Safe medicine disposal for ME program. University of Maine Center on Aging. Available: <http://www.safemeddisposal.com/>.

Vail J (2008). Disposing of Expired Drugs and Chemicals: New Options for Compounders. Internat J Pharm Compounding 12(1), 38-47.
WHO (1999). Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies. Organization WH. 31 p. Available:
http://www.who.int/water_sanitation_health/medicalwaste/pharmaceuticals/en/index.html.

NOTICE

Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.

Figure 1. Environmental Life Cycle of APIs [from: Daughton 2008]

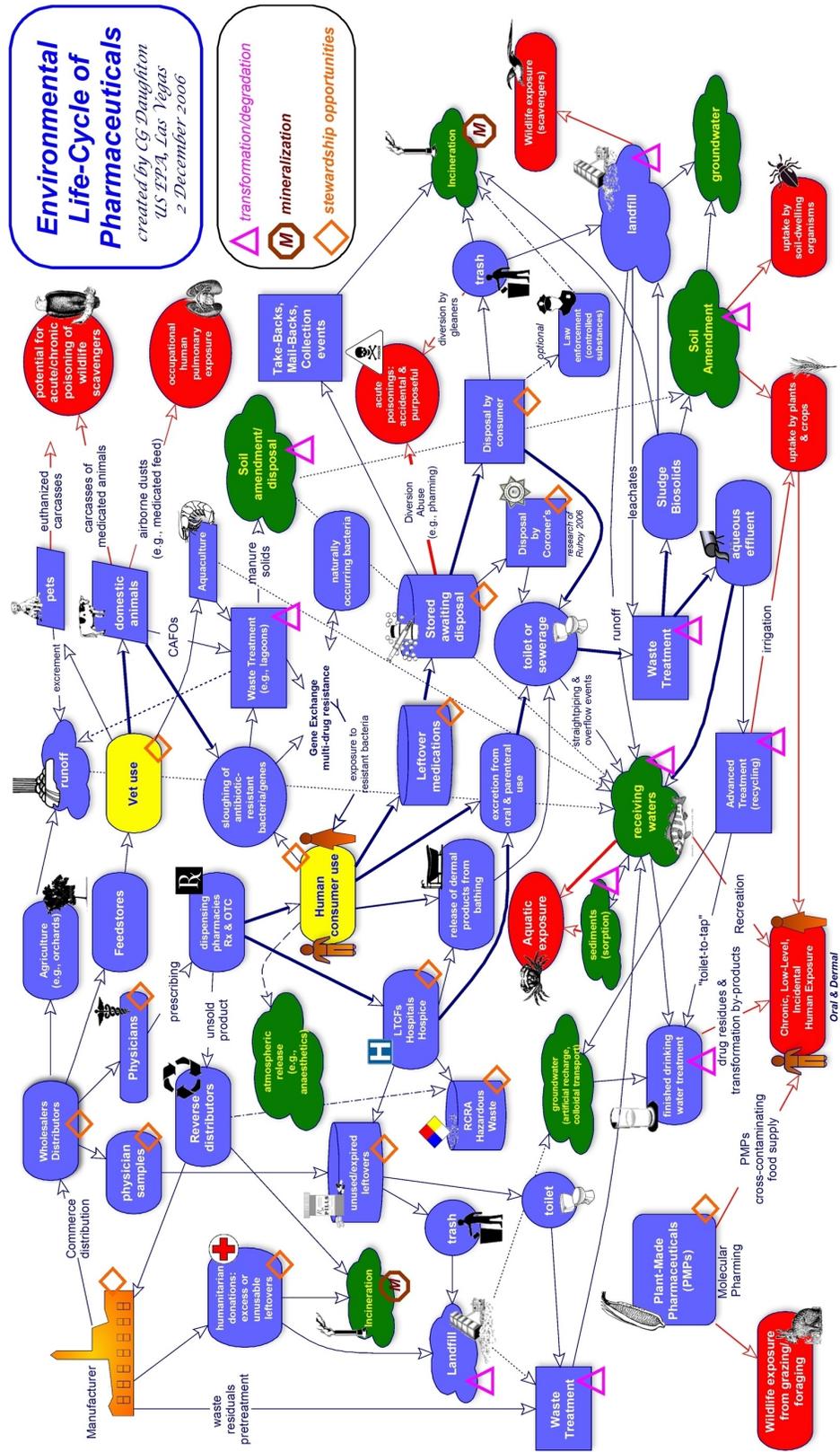


Figure 2. Accumulation and Disposal of Pharmaceuticals [from: Daughton and Ruhoy 2008a]

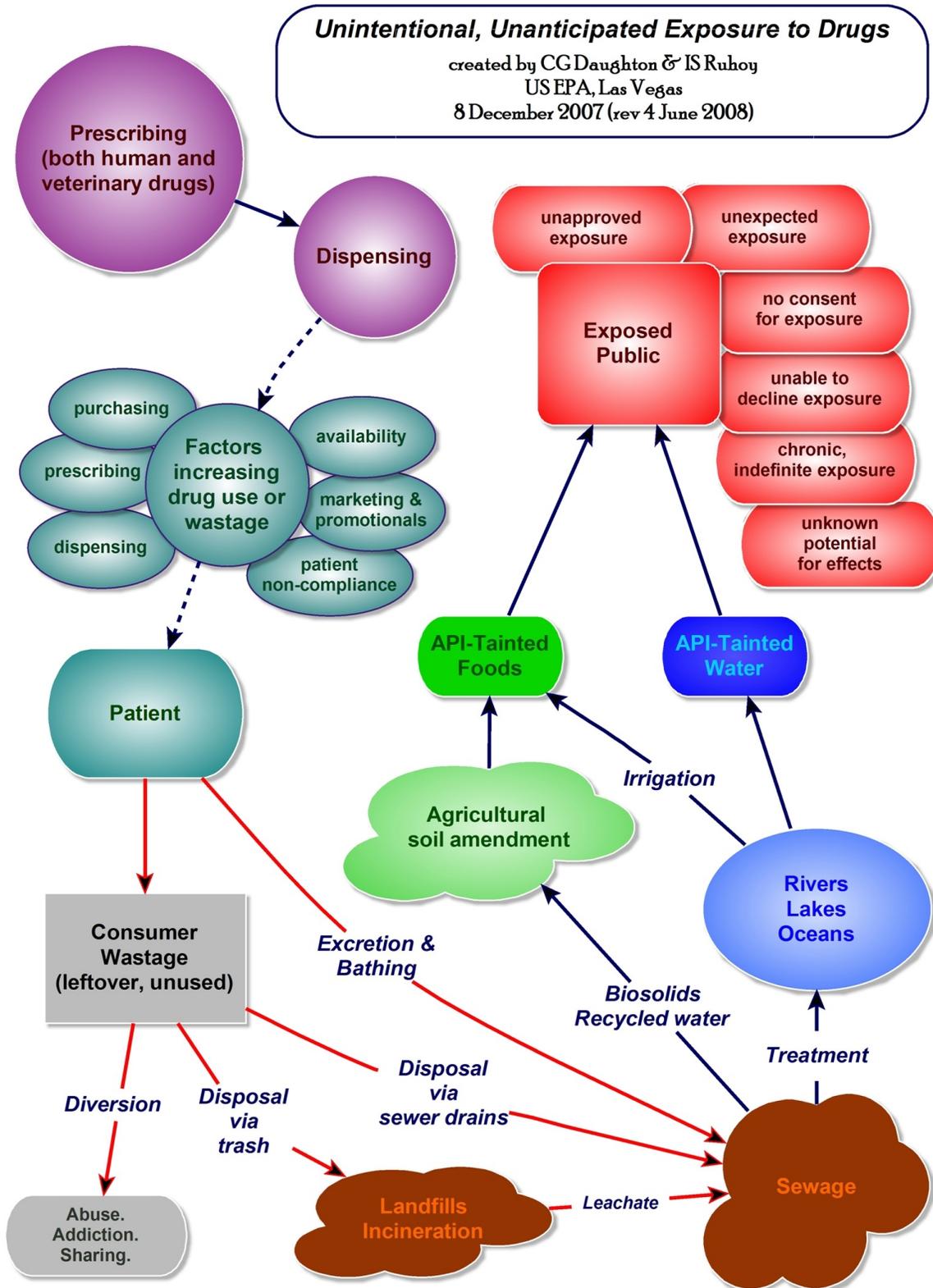


Figure 3. Factors Influencing Drug Consumption [from: Ruhoy and Daughton 2008]

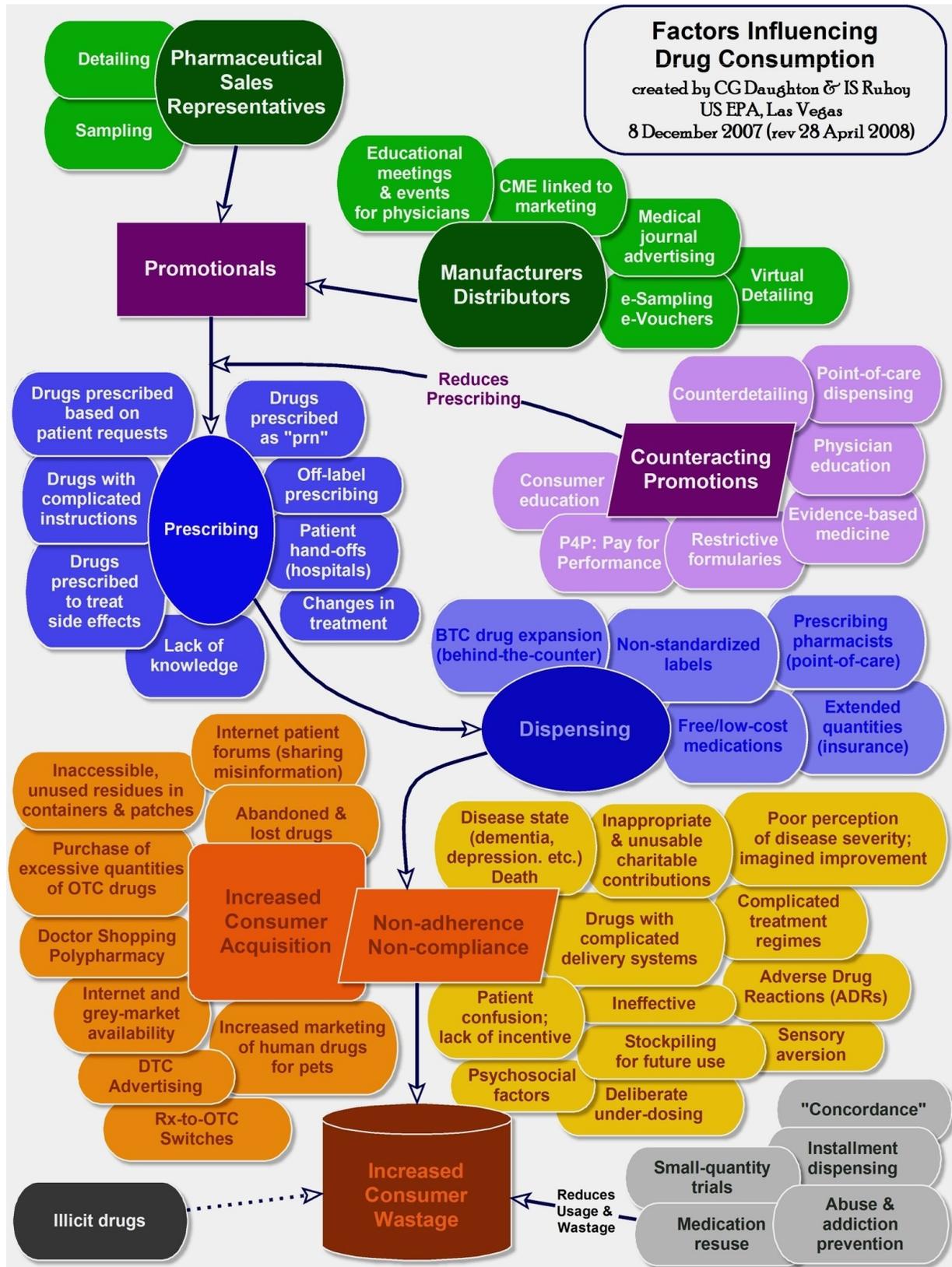


Figure 4. Points of Accumulation and Disposal of Drugs to the Environment [from: Ruhoy and Daughton 2008]

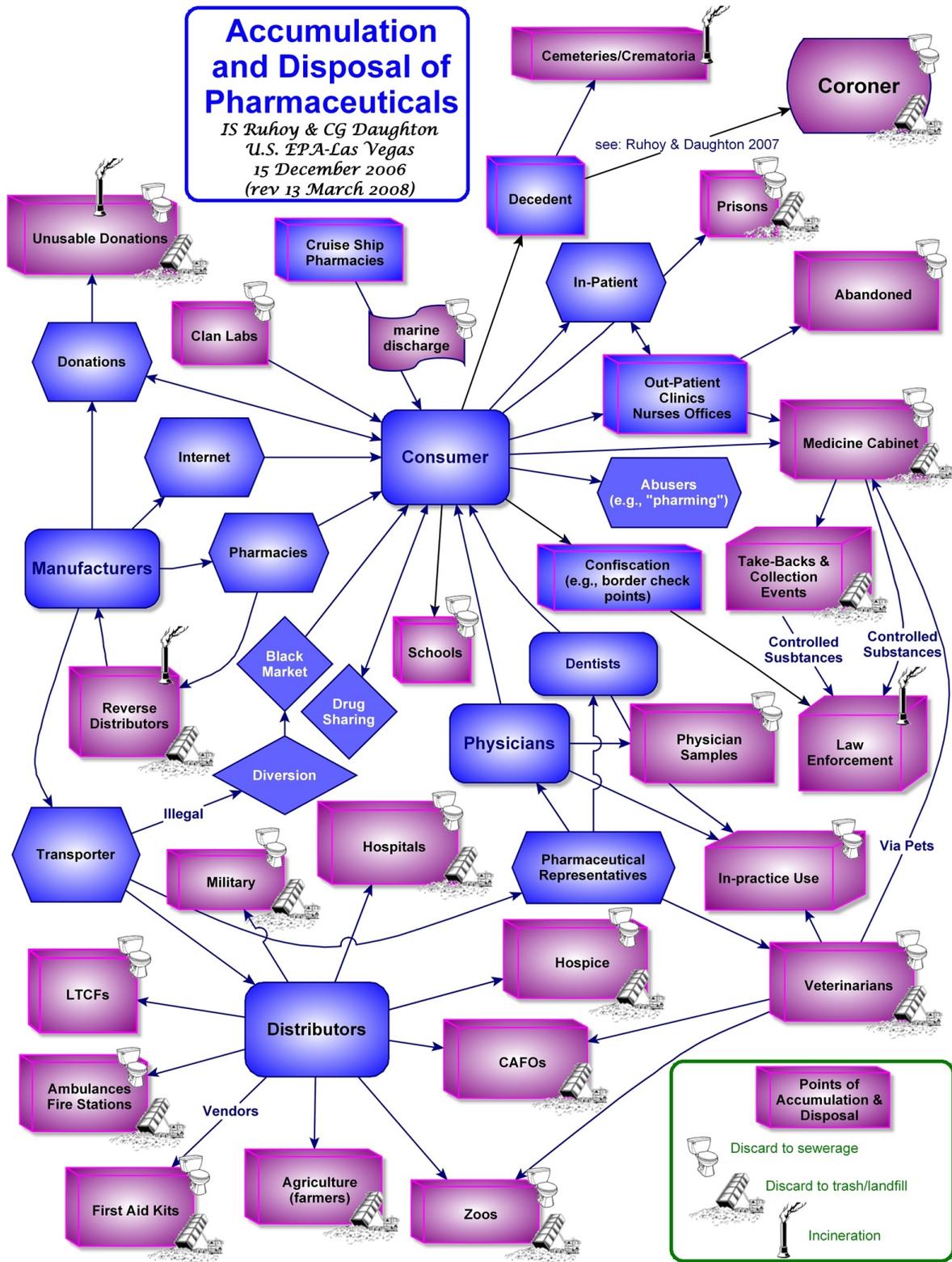


Figure 5. PharmEcoKinetics of APIs [from: Daughton and Ruhoy, 2008 submitted]

