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# **DOSED WITHOUT PRESCRIPTION: PREVENTING PHARMACEUTICAL CONTAMINATION OF OUR NATION'S DRINKING WATER**

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## LIST OF ABBREVIATIONS

AHI: Animal Health Institute  
AP: Associated Press  
APHA: American Public Health Association  
API: Active Pharmaceutical Ingredient  
AWWA: American Water Works Association  
CAA: Clean Air Act  
CAFO: Concentrated Animal Feeding Operations  
CCL: Candidate Contaminant List  
CCR: Consumer Confidence Report  
CDC: Centers for Disease Control  
CWA: Clean Water Act  
DEA: Drug Enforcement Agency  
DOD: Department of Defense  
EA: Environmental Assessment  
EDCs: Endocrine disrupting chemicals  
EDF: Environmental Defense Fund  
EE2: ethinylestradiol  
EPA: U.S. Environmental Protection Agency  
FDA: U.S. Food and Drug Administration  
FFDCA: Federal Food, Drug and Cosmetics Act  
GAO: U.S. Government Accountability Office  
HAP: Hazardous Air Pollutant  
HCWH: Health Care Without Harm  
IATP: Institute for Agriculture and Trade Policy  
KAW: Keep Antibiotics Working  
LTCF: Long term care facility  
NEPA: National Environmental Policy Act  
NMP: Nutrient Management Plan  
NRDC: Natural Resources Defense Council  
OTC: over-the-counter  
PAMTA: Preservation of Antibiotics for Medical Treatment Act  
PBT: Persistence, Bioaccumulation, Toxicity  
PDMA: Prescription Drug Marketing Act  
PhRMA: Pharmaceutical Research and Manufacturers Association  
ppb: parts per billion  
PSI: Product Stewardship Institute  
PSR: Physicians for Social Responsibility  
RCRA: Resource Conservation and Recovery Act  
SDWA: Safe Drinking Water Act  
SLEP: Shelf Life Extension Program  
UCMR: Unregulated Contaminant Monitoring Rule  
UCS: Union of Concerned Scientists  
USGS: U.S. Geological Service  
WHO: World Health Organization  
WWTP: Wastewater Treatment Plant

## I. Executive Summary

The presence of pharmaceuticals in our waterways and drinking water is a complex and potentially serious problem that has gained national attention with the public, lawmakers, and regulators. Some aspects of the problem are well-characterized, some are poorly characterized, and some are shielded from public scrutiny by industry. In this report we pull together information on the issue, including scientific data, legal analyses, and advocacy campaigns underway and identify what we consider to be the highest priority problems meriting additional attention from the funding, advocacy, and scientific communities.

Within the constraints of a six week time frame, the Natural Resources Defense Council (NRDC) researched the pharmaceutical industry from “cradle to grave” – that is, from the design and approval of drugs in the first place to the ultimate treatment and disposal of drugs when they are waste. We sought to examine how pharmaceuticals are contaminating our environment, highlight possible strategies to address the problem, and determine what organizations, if any, were pursuing those strategies.

Out of this research, we identified a “pipeline” with five main target areas where efforts could positively effect change: design, approval, production, use, and disposal. First, drugs could be designed to be fully metabolized by the body or to not persist in the environment. We found little activity in this area. Second, FDA approval processes could better consider environmental impacts. Again, there is little activity here. Third, the production of pharmaceuticals could be altered to generate less waste; green chemistry principles could be applied that reduce the generation of biologically active waste products. The pharmaceutical sector has, to some extent, begun to incorporate these concepts, but much more can be done. Fourth, the over-prescription and overuse of pharmaceuticals in both humans and animals can be tempered. There have been considerable advocacy and public education campaigns in this area: pressure on doctors to prescribe fewer drugs and a large number of activities to address the overuse of antibiotics in livestock. And finally, many different opportunities are available to prevent the discharge of pharmaceuticals into the aquatic ecosystem. We found a large number of initiatives focused on take-back programs to avoid intentional disposal down the drain, but little or nothing targeting the “unintentional” releases of drugs when excreted. Advocacy on the problem of animal farms and their discharge is also active.

In undertaking this research, we attempted to carve out where there are data available about the nature of this problem and where there are data gaps. We do know with certainty that diverse classes of pharmaceuticals are getting into our waterways and eventually into our tap water at levels that are detectable and in forms that are biologically active. Data collected by the U.S. Geological Survey and by individual municipal water utilities strongly suggest that pharmaceuticals are entering the environment and bypassing current treatment processes. We also know with certainty that the most important sources of these pharmaceuticals include those intentionally disposed into the sewer system, those discharged or released from livestock farms, and those that are excreted with human waste. And, we know with certainty that the lifecycle of pharmaceuticals—from production, to use, to excretion and disposal—generates significant excess that ends up as waste.

But more importantly, we were struck by substantial data gaps that leave very fundamental questions unanswerable at this time. We do not know the relative contribution of various sources to the total problem (human versus animal, intentional disposal down the drain versus excretion, etc.) either in general or even for individual classes of pharmaceuticals such as antibiotics. Also, we do not know the extent to which the concentrations found in drinking water or surface water affect human or

ecological health. Although there is a body of evidence that chemical contaminants in the water that harm aquatic and amphibious species include pharmaceuticals, no epidemiology studies have been done to link health outcomes with pharmaceutical contamination in water (and there is not likely to be any such data because of confounders and other almost insurmountable limitations in the experimental design). Moreover, there are no data that we uncovered concerning the toxicity of these compounds during incidental, lower-dose exposure to non-target populations.

We find that the most important knowledge gaps that should be addressed in any efforts to characterize the environmental and human health impact of pharmaceutical water contamination are as follows:

1. What volume (or magnitude measured by active units) of antibiotics is produced and used in the United States for medical, veterinary, animal production, and consumer product uses?
2. What volume (or magnitude measured by active units) of pharmaceuticals (and certain specific classes of pharmaceuticals) is present in our tap water and in our waterways?
3. Can these amounts cause or contribute to adverse human health effects, considering their presence as a complex mixture in drinking water and considering sensitive populations?
4. Is there a pharmaceutical class or category of greatest concern?
5. What proportions of pharmaceutical contaminants (and certain classes of pharmaceuticals) come from excretion from humans versus disposal down the drain?
6. What is the relative contribution from animal uses, especially the use of antibiotic and growth hormone drugs in concentrated animal feeding operations (CAFOs), to overall pharmaceutical contamination levels?
7. What magnitude of waste per unit of desired product comes from manufacturing pharmaceuticals (and certain classes of pharmaceuticals), and how much of this waste is active ingredient, hazardous chemicals, or biological hazardous waste?
8. What is the best disposal method to protect the environment? Is disposal in landfills a significant source of contamination?
9. How persistent are pharmaceuticals (and certain classes of pharmaceuticals) in the environment, and how effective are conventional wastewater treatment and drinking water treatment in destroying them?

While the issue of pharmaceutical contamination of drinking water has only been recently introduced to the general public, it has been recognized for over a decade among scientists, environmentalists, and other public interest groups. This report strives to identify what problems arise in each segment of the lifecycle, what we know and what we still need more information about, and what public interest groups are doing and can do to address these gaps.

Of course, even in light of the environmental impacts of pharmaceuticals, we would not advocate against the development or prescription of medications when medically necessary. Medical professionals – especially reproductive health professionals – are rightly worried that over-emphasis on the impacts of synthetic estrogen on the environment could discourage or limit women's access to birth control and reproductive choice. We do not want to eliminate the use of life-saving drugs, nor do we want to single out those people who need them. Therefore, the strategies and recommendations that we offer below are focused on making each step of the process cleaner, not to eliminate the pharmaceutical sector or create pressure against valuable drugs.

## II. Introduction

In March 2008, the Associated Press (AP) reported that pharmaceutical residues were detected in the drinking water of 24 major metropolitan areas across the country serving 41 million people.<sup>1</sup> This information was derived from tests that water utilities had undertaken voluntarily and provided to the press. Detected drugs included antibiotics, anti-convulsants, and mood stabilizer drugs. These results supported previous findings of the U.S. Geological Survey that sampled 139 streams in 30 states in 1999-2000 and found organic wastewater contaminants and pharmaceuticals in 80 percent of sampled sites – including antibiotics, hypertensive and cholesterol-lowering drugs, antidepressants, analgesics, steroids, caffeine, and reproductive hormones.<sup>2</sup> In fact, as analytical technology has allowed for the detection of even lower concentrations of pharmaceuticals in aquatic systems, it has become clear that these contaminants are ubiquitous.

The unintended movement of biologically active, toxic, and hormone-disrupting compounds from pharmaceuticals to wastewater effluents and drinking water sources is an international problem that has been documented and publicly reported by government experts and academic researchers for nearly two decades.<sup>3</sup> However, until the AP report, the general public had been in the dark about the presence of these chemicals in our drinking water.

This report, which was motivated by the release of the AP findings, seeks to identify what is known about the sources of pharmaceutical contamination of water, and the magnitude of the risks that that contamination poses, as well as to document on-going efforts to address the problem and make recommendations for further research and advocacy.

### A. SCOPE OF THE PROBLEM

Pharmaceuticals include human and veterinary drugs (both prescription and over-the-counter), medical agents such as chemotherapeutic drugs, and x-ray contrast media. These materials may end up in the environment through manufacturing waste, waste from human or animal excretion, improper disposal such as flushing down a toilet, runoff from animal feeding operations, or leaching from municipal landfills. Indirect pathways of entry to the environment are also problematic. For example, as water resources are depleted, particularly in the arid United States, reclaimed wastewater is becoming an increasingly important source for irrigation. The problem is that pharmaceuticals can enter the soil and potentially contaminate groundwater when contaminated wastewater is reclaimed and used for irrigation.

Perhaps one of the most common pathways through which pharmaceuticals enter the environment is human consumption, followed by excretion to a sewage treatment plant and release to surface water as wastewater effluent. Veterinary use, both in large farming operations and in aquaculture, is the other significant contribution to the problem.

For a number of reasons – including historical practice, convenience, or ignorance – many people and institutions flush unused and unwanted pharmaceuticals down the toilet. There is little data available to calculate the relative contribution of improper disposal of pharmaceuticals (intentional releases) to the total release into the environment. We found only one estimate: that improper disposal of unused pharmaceuticals contributes up to one-third of the total load of pharmaceuticals in the environment, but this estimate was provided in a paper presented at a conference and not in a peer-reviewed journal.<sup>4</sup>

Furthermore, surprisingly little work has been done to evaluate the detrimental effects of exposure to low levels of pharmaceuticals on human health. Environmental concentrations are generally several orders of magnitude below therapeutic doses, but such low level exposures could nonetheless pose risks, particularly to sensitive sub-populations such as the fetus, people with chemical sensitivities, or people with existing disease burdens that could be exacerbated by inadvertent exposures (such as patients suffering from endocrine-related cancers).<sup>5</sup> Assessing possible effects is greatly complicated by the fact that environmental contaminants are always present as mixtures.

The pharmaceutical industry has contributed to the debate on this topic. In the late 1990s, the Pharmaceuticals Research and Manufacturers of America (PhRMA), the trade association for pharmaceutical companies, established the Pharmaceuticals in the Environment Task Force. This task force has developed working groups around the issue of pharmaceuticals in the environment, specifically looking at fate and transport, human health effects, environmental risk assessment, hormones, unused medicines, treatment, and communications.<sup>6,7</sup> The group maintains that the industry is committed to evaluating the risk of pharmaceuticals in the environment using a science-based approach. Currently, they believe that all of the pharmaceutical compounds tested to date pose no “appreciable risk” to human health in drinking water.<sup>8</sup> However, beyond the clinical trials that test exposure to one drug at a time, they have not provided any evidence of this “no appreciable risk” with low dose mixtures or at chronic exposures outside of a controlled clinical trial. Better coordination to provide already generated data to environmental agencies could help with this problem. PhRMA itself is still in the process of evaluating the effects of pharmaceuticals on aquatic life and ecosystems. However, they have decided that disposing unused drugs down the drain should be avoided and are continuing to research the sources of unused medicine and the most environmentally conscious methods to dispose of them.<sup>9</sup>

Notably, the European community has also begun looking into and dealing with pharmaceuticals in the environment. In late 2008, the European Commission began a project known as Knowledge and Need Assessment of Pharmaceutical Products in Environmental waters to try to fill these informational gaps.<sup>10</sup>

## **1. Priority Pharmaceuticals of Concern**

Several categories of pharmaceuticals raise particular concerns: those produced and consumed in especially large quantities, those highly potent at low concentrations, and those particularly persistent and bioaccumulative in the environment. Within these categories, two types of pharmaceuticals – antimicrobials and endocrine disrupting chemicals (EDCs) – can be appropriately singled out as priorities.

### ***Antimicrobials***

The migration of antimicrobials into the environment has significant impacts. They can disrupt wastewater treatment processes and adversely affect ecosystems because they are toxic to beneficial bacteria. Some antimicrobials also bioaccumulate; for example, erythromycin has been found to have both a high bioaccumulation factor of 45.31 and a tendency to accumulate in soils.<sup>11,12</sup> Antimicrobials can also be persistent for extended periods of time; the environmental persistence of erythromycin, for example, is longer than one year.<sup>13</sup>

Although not well-studied, the presence of antimicrobials in natural waters may be exerting selective pressure leading to the development of antibiotic resistance in bacteria. The threat of growing antibiotic resistance has been recognized by, among others, the World Health Organization (WHO), the National Academy of Sciences (NAS), the American Medical Association (AMA), the American

Public Health Association (APHA), and the U.S. Government Accountability Office (GAO). In fact, the Centers for Disease Control and Prevention (CDC) has identified antibiotic resistance as one of the most pressing public health problems facing our nation.<sup>14</sup> Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year.<sup>15</sup> Methicillin-resistant strains of *Staphylococcus aureus*, although previously limited primarily to hospital and health facilities, are becoming more widespread.<sup>16</sup> In 2007, Consumer Reports tested over 500 whole chickens for bacterial contamination and antibiotic resistance. They found widespread bacterial contamination in their samples and 84 percent of the salmonella and 67 percent of the campylobacter organisms that were isolated showed resistance to one or more antibiotics.<sup>17</sup>

Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Half of the antibiotics used in livestock are in the same classes of drugs that are used in humans.<sup>18</sup> The U.S. Institute of Medicine and the WHO have both stated that the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in pathogens that affect humans.<sup>19</sup>

Further exacerbating the problem, antimicrobials are considered “high production volume chemicals,” meaning they are produced or imported at well over 1 million pounds annually. In fact, the industry trade group for animal use of antibiotics reports that in 2006, U.S. sales of antibiotics just for animal uses exceeded 26 million pounds.<sup>20</sup>

### ***Hormones and endocrine disrupting drugs***

The second class of troubling pharmaceuticals are hormones and endocrine disrupting drugs, which are excreted as waste by-products from the use of, among others, birth-control pills, menopause treatments, thyroid replacement, and cancer therapy. For example, one synthetic hormone found in environmental samples is ethinylestradiol (EE2), which is found in some oral contraceptives and has been implicated in the feminization of fish in international waterways.<sup>21</sup> EE2 is extremely potent at very low concentrations; laboratory studies predicted that a concentration of 0.1 ng/L in surface water could induce production of the female egg protein vitellogenin in male rainbow trout.<sup>22</sup> In addition, EE2 has been found to bioaccumulate, reaching concentrations of up to one million times higher in fish than in the surrounding water.<sup>23</sup> However, the synthetic estrogen used in oral contraceptives has been estimated to contribute only one percent to the total amount of estrogens excreted by humans.<sup>24</sup> Therefore, other sources of synthetic hormones must be investigated before blaming oral contraceptives as the main culprit.

In addition to human uses, steroids are widely used in livestock operations and contribute to widespread environmental contamination. Beef cattle raised in large feedlots are treated with anabolic steroids to promote the growth of muscle. One of the most common steroids used is a male sex hormone (androgen) mimic, trebolone acetate. Exposure to trebolone metabolites at concentrations as low as parts per trillion can cause masculinization of female fish and reduced fertility.<sup>25</sup> A recent study at an Ohio-based animal feeding operation with a capacity for 9,800 cattle found detectable concentrations of trebolone in the discharge from the facility at levels that were sufficient to induce gene expression associated with exposure to androgens.<sup>26</sup> Humans are also sensitive to low levels of sex hormones; in fact, sex hormones in all vertebrate species work in the parts per billion to parts per trillion range.<sup>27</sup> These pharmaceuticals interfere not only with sex hormones but also with other hormonal systems including the thyroid gland, which is critical for proper growth and development of the brain during fetal growth, infancy, and childhood.

Other categories of pharmaceuticals that may be of concern because of their high production volume include lipid regulators, anti-inflammatories and analgesics, antiepileptics, and selective serotonin reuptake inhibitors.<sup>28</sup>

Appendix A provides a table that summarizes the patterns of occurrence of various priority pharmaceuticals in water.

## **2. Ecological Priorities**

The presence of pharmaceuticals in drinking water also raises issues beyond the obvious concern about public health. Ecologically, pharmaceutical chemicals in waterways threaten wildlife with continuous exposures. Since human exposures through drinking water are more intermittent, some experts have identified ecosystem effects as a higher concern than human health.<sup>29</sup>

Environmental monitoring has identified a number of pharmaceuticals, including ibuprofen, acetaminophen, carbamazepine, gemfibrozil, mefenamic acid, and oxytetracycline, present in some environments at levels high enough to harm aquatic organisms.<sup>30</sup> Severe effects from exposure to relatively low levels of some pharmaceuticals are possible, as shown by the recent discovery that vultures in Asia have been dying from eating cattle containing relatively low concentrations of the drug diclofenac.<sup>31</sup> Permanent developmental abnormalities have also been suspected with mounting evidence that the contamination of waterways are causing intersex fish in our nation's rivers and drinking water sources. For example, the U.S. Geological Survey (USGS) reported a high incidence of intersex fish in the Potomac watershed at sites of intense farming and high human population density.<sup>32</sup> Specifically, the USGS found that 75 percent of male smallmouth bass in the most densely populated and heavily farmed Potomac basin had eggs in their testicles. Other research has found environmental androgens associated with masculinization in female fish living downstream of pulp mills and concentrated animal feeding operations.<sup>33</sup>

The ecological impacts – such as the likelihood of adverse effects on aquatic organisms and persistence of certain chemicals in the environment – can be the basis for developing a priority list of pharmaceuticals. For example, Doerr-MacEwen developed a priority list of some of the most commonly detected pharmaceuticals that represent the greatest concern for environmental impact, accounting for these factors and the chemicals' recalcitrance to treatment.<sup>34</sup> (See Appendix B for the prioritization table.) Also, a WikiPharma has recently been published which compiles publicly available ecotoxicity data for APIs into a free database.<sup>35</sup>

## **B. SIZE AND NATURE OF THE PHARMACEUTICAL INDUSTRY**

Year after year, the pharmaceutical industry continues to be among the most profitable of all businesses in the United States, topping the annual Fortune 500 survey of the most profitable industries.<sup>36</sup> While there was little to no growth in other top industries, the pharmaceutical industry self-reported continuing growth in the United States.<sup>37</sup> The top pharmaceutical companies are shown in **Table 1**.

**Table 1. Top Pharmaceutical Companies, Ranked by Total Revenue, Based on Reported Data from Industry Annual Reports<sup>38</sup>**

Rank (2006)	Company	Country	Total Revenue (US\$ B)	Pharmaceutical Sales 2007 (US\$ B)	Animal Health Sales* 2007 (US\$ B)
1	Johnson & Johnson	USA	61.1	24.9	0
2	Bayer	Germany	51.5	16.4	1.5
3	Pfizer	USA	48.4	44.4	2.6
4	Hoffmann-LaRoche	Switzerland	45.4	36.2	0
5	GlaxoSmithKline	UK	45.2	38.3	0
6	Sanofi-Aventis	France	44.6	40.2	0
7	Novartis	Switzerland	39.8	24	<5.2
8	AstraZeneca	UK/Sweden	29.6	28.7	0
9	Abbott Laboratories	USA	25.9	14.6	<1.5
10	Merck & Co.	USA	24.2	20.1	2.4
11	Wyeth	USA	22.4	18.6	1
12	Bristol-Myers Squibb	USA	19.3	15.6	0
13	Eli Lilly and Co	USA	18.6	17.6	1
14	Boehringer Ingelheim	Germany	17.4	16.7	0.7
15	Amgen	USA	14.8	14.3	0
16	Schering- Plough	USA	12.7	10.2	1.3

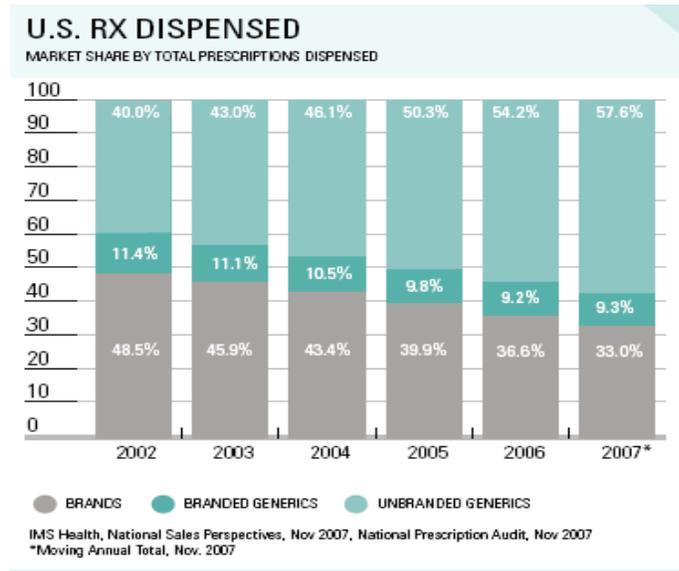
\* Note that animal health pharmaceutical use, mainly antibiotics, is discussed in more detail below. Also, note that many of these companies represent many of the major producers of animal pharmaceuticals.

Big “blockbuster” drugs bring in a lion’s share of the total revenue to these firms. Among those blockbuster drugs are Pfizer’s cholesterol pill Lipitor (one of the best-selling drugs in the world), Plavix (the blood thinner from Bristol-Myers Squibb), Sanofi-Aventis, Nexium (the heartburn pill from AstraZeneca), and Advair (the asthma inhaler from GlaxoSmithKline).<sup>39</sup>

However, as well known as these drugs are, generics may be an equally important – if not more important – segment of the pharmaceutical industry. Generics only account for 20.5 percent of all types of prescription sales in the United States because of their relatively low price, but they represent 65 percent of the total amount of prescriptions dispensed.<sup>40 41</sup> (See Figure 1.) In 2007, many of the top 20 generic drugs sold twice the total units as the top 20 brand name drugs, and this segment of the market is growing by seven percent annually, faster than the total.<sup>42</sup> (See Table 2.)

Interestingly, the top generic companies are either among the largest pharmaceutical companies overall (Teva Pharmaceuticals is among the top 20) or they are subsidiaries of large pharmaceutical companies (for example, Sandoz is a Novartis company).

**Figure 1 U.S. Prescriptions Dispensed**



**Table 2. Prescriptions of Generic Product and Brand Name Product Sold in the United States in 2007<sup>43</sup>**

Top Generic Products	Units Sold	Top Brand Name Products	Units Sold
Hydrocodone/APAP	117,200	Lipitor	55,122
Lisinopril	61,704	Singular	27,255
Amoxicilin	52,987	Lexapro	27,023
Levothyroxine	49,677	Nexium	26,425
Hydrochlorothiazide	45,777	Synthroid	25,526
Azithromycin	45,279	Plavix	22,336
Atenolol	42,180	Toprol XL	21,042
Simvastatin	41,496	Prevacid	20,397
Alprazolam	40,914	Vytorin	19,396
Furosemide Oral	37,094	Advair Diskus	18,181
Metformin	36,786	Zyrtec	17,936
Sertaline	28,037	Effexor XR	17,200
Metoprolol Tartrate	27,486	Protonix	16,066
Ibuprofen	24,656	Diovan	15,199
Amlodipine Besylate	23,489	Fosamax	15,096
Oxycodone w/APAP	23,443	Zetia	14,264
Prednisone Oral	23,053	Crestor	13,758
Cephalexin	22,354	Levaquin	13,553
Fluoxetine	22,266	Diovan HCT	12,868
Triamterene w/HCTZ	21,335	Klor-Con	12,788
<b>Total:</b>	<b>787,213</b>	<b>Total:</b>	<b>411,431</b>

**Table 3. The Largest Generic Pharmaceutical Companies by Sale and Prescriptions<sup>44</sup>**

Rank	Sales (\$ constant)	Volume (Prescriptions)
1	Teva Pharmaceuticals USA	Teva Pharmaceuticals USA
2	Sandoz (Novartis)	Mylan Laboratories
3	Mylan Laboratories	Sandoz (Novartis)
4	Watson Pharmaceuticals	Watson Pharmaceuticals
5	Greenstone (Pfizer)	Barr Laboratories
6	Par Pharmaceuticals	Mallinckrodt
7	Apotex	Greenstone (Pfizer)
8	Barr Laboratories	Qualitest Products
9	Roxane (Boehringer Ingelheim)	Actavis USA
10	Hospira	Par Pharmaceuticals

In 2006, global spending on prescription drugs topped \$643 billion, despite slowed growth in Europe and North America. With \$289 billion in annual sales, the United States accounts for almost half of the global pharmaceutical market, followed by the European Union and Japan. However, the growth in emerging markets such as China, Russia, South Korea, and Mexico outpaced that market; all reached double digits, outpacing the global market.<sup>45</sup>

In addition to manufacturing human pharmaceuticals, many of the brand name companies produce pharmaceuticals for animal use, such as Novartis, Pfizer, and Lilly, although many livestock drugs are manufactured by smaller companies.<sup>46</sup> Notably, as discussed above, livestock drugs are dominated by antibiotics.

The quantity of antibiotics manufactured and used in animals is poorly understood, and estimates vary depending on the source of the data. Based on data from 2002, the GAO, the investigative arm of Congress, estimated that about 13 million pounds of active pharmaceutical ingredients (API) are sold for animal use (not including ionophores).<sup>47</sup> Based on a 1998 survey, the Animal Health Institute (AHI), the trade association representing 80 percent of industries producing antibiotics for animals, estimated that 18 million pounds were sold for all animal uses in that year.<sup>48</sup> And these figures appear to be growing. More recently, the AHI reported that U.S. sales of antibiotics for both livestock and companion animals totaled 24.4 million pounds in 2005, 26.5 million pounds in 2006, and 27.8 million pounds in 2007.<sup>49</sup> The AHI also reported rapid growth in the sales of animal antibiotics – 8.2 percent between 2005 and 2006. The increase in sales was primarily due to two classes of antibiotics, tetracyclines (also used in humans) and ionophores (not used in humans). However, these figures may significantly underestimate the use of antibiotics in animals. A study published by the Union of Concerned Scientists (UCS) in 2001 estimated that non-therapeutic use of antibiotics in cattle, swine, and poultry alone totaled 24.6 million pounds.<sup>50</sup>

Both the AHI and the UCS have similar estimates for the total volume of sales of antibiotics. The groups diverge in their estimate of the portion of antibiotics used for animals versus humans. The AHI trade group argues that their members use approximately one-third of the total volume of antibiotics, whereas the UCS itself estimates that it is over two-thirds.<sup>51</sup> Since neither industry nor the government provide adequately detailed, publicly available sales and market share data, more reliable calculations are not possible. This serious failure of government to require comprehensive data, collected regularly, and presented to the public in standardized formats, prevents regulators,

the public, and Congress from making informed decisions on how best to reduce pharmaceutical contamination. This lack of reliable detailed data plagues this entire report.

Table 4 shows the major antibiotics sold in 2006 for animal use. These drugs are mainly used in swine and poultry (about ten million pounds each), with much less used in cattle (about 3 million pounds).<sup>52</sup>

**Table 4. Major Animal Antibiotics Sold**

<b>Antibiotic</b>	<b>2006 (million pounds)</b>	<b>2007 (million pounds)</b>
Ionophores, arsenicals, bambarmycin, carbadox, and tiamulin	11.1	10.6
Tetracyclines	9.2	10.7
Cephalosporins, macrolides, lincosamides, polypeptides, streptogramins, fluoroquinolones, and other minor classes of antibiotics	4.4	4.5
Sulfonamides and penicillins	1.2	1.8
Aminoglycosides	0.33	0.20

The continuing growth of the pharmaceutical industry foretells the continuing movement of these contaminants into our global aquatic environment and a rich industry that may be reluctant to trade its profits for better stewardship programs. Therefore, the United States' large contribution to the growth of the industry through consumption as well as some production could be leveraged to achieve global improvements in the manufacturing processes and disposal practices.

### **C. THE PIPELINE OF OPPORTUNITIES**

A systematic look at the entire lifecycle of pharmaceuticals reveals five main target areas where efforts could positively affect change:

Design: At the outset of developing a new pharmaceutical, the design could be greatly improved by considering the inherent environmental impacts of the drug. Efforts to maximize absorption into the body and dose the chemical more precisely to individual patient weight, for example, could be very helpful in reducing unintentional discharge in urine and feces. The PBT profile (persistence, bioaccumulation, and toxicity) should become an integral part of the drug discovery process.

Approval: In obtaining FDA approval to market a drug, manufacturers often provide cursory statements about possible environmental impacts. These procedures could be revamped so that the environmental impacts are considered more substantively, at least for drugs with the greatest potential to cause harm.

Production: The production of pharmaceuticals usually results in up to thousands of pounds of waste for each pound of product. A pollution prevention assessment of upstream opportunities to reduce waste prior to treatment could clarify how much of this waste is really necessary.

Use: The over-prescription of pharmaceuticals in humans and the over-use of antibiotics in animals is a core contributor to the problem of pharmaceuticals in drinking water. Efforts to curtail these

practices would have beneficial secondary effects with respect to the development of antibiotic resistance and other public health matters.

Discharge and Disposal: The discharge and disposal of pharmaceuticals is an end-of-the-pipe problem without many answers. Identification of best practices for treatment of compounds of highest concern as well as collection initiatives for unused and expired pharmaceuticals would illuminate paths forward for improvement.

This report systematically explains each of these steps and attempts to address the relevant issues associated with each stage. Ultimately, this report identifies opportunities for change and recommendations to consider at each stage in the lifecycle.

In the end, it is paramount that we continue to foster an environment where sick patients have access to life-saving medicines and where women have access to birth control and reproductive choice. The issues raised in this report are not meant to prioritize environmental considerations over medical concerns. Rather, the recommendations offer substantive changes that can be made to improve the design, approval, production, use, and discharge or disposal of pharmaceuticals in ways that allow for the continued use of safe and effective medicine, while also protecting the environment from unnecessary harm.

### **III. Legal Framework**

The manufacture, collection, and discharge and disposal of pharmaceuticals are regulated by a number of different federal laws and by three different federal agencies – the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the Drug Enforcement Agency (DEA). The U.S. Department of Agriculture provides guidance for animal waste management (quantity and storage), but regulating the environmental impacts of waste is deferred to the EPA.

#### **A. FOOD AND DRUG ADMINISTRATION**

The Federal Food, Drug and Cosmetics Act of 1980 (FFDCA) empowers the FDA to regulate pharmaceuticals that are not generally recognized as safe and effective. Under this Act, the FDA is responsible for reviewing the potential environmental impact from the intended use of human and veterinary medicines. To evaluate the potential effects of a proposed compound, the FDA requires the submission of an Environmental Assessment (EA), pursuant to the National Environmental Protection Act (NEPA).<sup>1</sup>

NEPA requires federal agencies to conduct environmental impact assessments of any federal action that may significantly affect the human environment.<sup>2</sup> Under NEPA, the approval of a drug that triggers the requirements to conduct an EA is considered a “federal action.” (The EPA does not have authority to review drugs because drugs are specifically exempted from the Toxic Substances Control Act.)

While EAs are required for all new drug applications and some supplementary submissions, they have historically consisted of little more than a statement that a compound had no potential environmental impact. The FDA has recently increased and intensified the EA review and approval process under which it now requires quantitative documentation of a compound's potential environmental impact, including studies identifying the actual component of the drug that will enter the environment, the toxicity of that component, the likelihood of the drug to amass in the aquatic environment, environmental depletion mechanisms, expected introduction concentration, and expected environmental concentration.<sup>3</sup>

However, because NEPA does not require that the most environmentally beneficial course of action be taken, it is unlikely that this authority would adequately restrict pharmaceuticals from the environment. Furthermore, the FDA has a number of categorical exclusions to the EA requirement, most notably exempting from review the production of drugs predicted to occur at less than one ppb in the aquatic environment or 100 ppb in soil, which likely excludes many drugs<sup>4</sup>.

#### **B. ENVIRONMENTAL PROTECTION AGENCY**

The EPA regulates discharges to water from the pharmaceutical industry and from sewage treatment plants under the Clean Water Act and industrial emissions to air under the Clean Air Act. In addition, the EPA regulates the disposal of pharmaceutical manufacturing waste under the Resource Conservation and Recovery Act.<sup>5</sup> The Safe Drinking Water Act gives the EPA the authority to set health-based standards for certain contaminants that are present in drinking water.<sup>6</sup>

##### **1. Clean Water Act (CWA)**

Under the CWA, pharmaceutical manufacturers who discharge directly into receiving waters must have individual National Pollution Discharge Elimination System (NPDES) permits, which are

issued subject to regulations called Effluent Guidelines and Standards for Pharmaceutical Manufacturing Point Source Categories.<sup>78</sup> Generally, the regulations require monitoring and reporting for each regulated pollutant that is either an ingredient or that is used in the manufacturing process.<sup>9</sup> For pharmaceutical manufacturing, these pollutants include the components of the formulations, the chemical intermediaries, or the final pharmaceutical product.<sup>10</sup> Water is tested at the outflow, whether that outflow is to a municipal wastewater system or directly into the environment. Those who discharge to publicly owned treatment works (that is, sewer companies) must comply with National Pretreatment Standards. Since publicly owned treatment works must apply for NPDES permits, the EPA could regulate the amount of pharmaceuticals that are discharged by those plants.

However, these limitations may not be strict enough to protect human health and the environment because they are technology-based. As explained later, there is no treatment technique currently available that comprehensively deals with all pharmaceuticals.

## **2. Clean Air Act (CAA)**

The EPA also regulates pharmaceutical manufacturers under the CAA, specifically by the regulations governing Emission Standards for Hazardous Air Pollutants (HAPs).<sup>11</sup> Manufacturing facilities that use compounds that produce HAPs are required to test for and control emissions from exhaust stacks and the so-called “fugitive emissions” that escape from equipment, filters, poorly welded pipe joints, and other non-stack sources. These regulations do not apply to all manufacturing facilities, but rather to certain major stationary sources that meet certain emission levels.

For many reasons, the CAA is not a useful tool for regulating pharmaceuticals in the environment. First, none of the chemicals that fall under the HAP regulations are APIs.<sup>12</sup> Second, as with the water standards and limitations for manufacturing operations under the CWA, it is unlikely that much of the contamination currently being found in drinking water originates in air emissions from manufacturing facilities. Finally, even if APIs were added to the HAPs list, reporting requirements for certain HAPs begin when a facility has the capability of emitting ten tons of any one HAP or 25 tons of any combination, and it is unlikely that any facility will emit such high amounts of API.<sup>13</sup>

## **3. Resource Conservation and Recovery Act (RCRA)**

Any pharmaceuticals that are characterized as hazardous or listed materials are regulated by the EPA under RCRA, the federal law that regulates the management of solid waste, including hazardous waste.<sup>14</sup> However, a number of pharmaceuticals have developed since RCRA was enacted, including perhaps one hundred chemotherapy drugs that should be but are not regulated as hazardous. Those that are listed as hazardous, if generated in large enough quantities, would be regulated if disposed of by a hospital or other medical facility.<sup>15</sup> Pharmaceuticals that are disposed of unused and are explicitly designated as acutely hazardous (P-listed) or toxic (U-listed) by the RCRA regulations are considered hazardous materials and must be disposed of accordingly. Because RCRA exempts residential or household users from their regulations, pharmaceuticals are not regulated by the EPA if they are disposed of by an individual.<sup>16</sup>

## **4. Safe Drinking Water Act (SDWA)**

The SDWA governs the regulation of contaminants in our drinking water supplies. Pursuant to the SDWA, the EPA sets health-based standards to restrict the amount of certain contaminants that may appear in drinking water. To date, the EPA has not established any standards under the SDWA for pharmaceuticals. The SDWA does, however, contain four provisions under which pharmaceuticals could be considered for regulation.

First, the SDWA created a system that would push the EPA to determine whether there are unregulated contaminants that should be regulated. As such, the EPA must, every five years, publish a list of currently unregulated contaminants that should be considered for potential regulation, called the Contaminant Candidate List (CCL). The EPA must then make a final determination about whether or not to regulate at least five of the contaminants identified on the CCL. The CCL listing process has gone through three iterations, beginning in 1998 with the publication of CCL1 and then CCL2 in 2005. Shortly before publication of this white paper, the EPA finalized its third CCL. In response to the public outcry about pharmaceuticals in the environment, the EPA included, for the first time, eleven chemicals that are found in pharmaceuticals.” However, to date, no chemical has ever been selected for regulation through the CCL process, and it remains an ineffective process for listing contaminants for regulation.

Second, the SDWA established a process to inform both the determination of whether to regulate a contaminant on the CCL, and whether or not a contaminant should even be listed on the CCL. Specifically, public water systems are tasked with collecting monitoring data on unregulated contaminants to help the EPA decide whether or not to regulate a given contaminant. In 1999, the EPA promulgated an unregulated contaminant monitoring rule (UCMR) that imposed various monitoring requirements on community water systems for a list of unregulated contaminants. The first round of the UCMR consisted of 26 unregulated contaminants that required some amount of monitoring data. The second UCMR identified an additional 24 unregulated contaminants not identified by the first UCMR. None of the unregulated contaminants that water systems are required to monitor are pharmaceuticals.

Third, in recognition of the public’s right to know, the SDWA requires community water systems to mail to each of their customers an annual report on the level of contaminants in the drinking water that they supply. These consumer confidence reports (CCRs) must contain, among other things, information on the source of the water, detections of regulated contaminants in the water, and levels of unregulated contaminants found in the water (those unregulated contaminants identified by the UCMR). However, because pharmaceuticals do not appear on any regulated or unregulated contaminants lists, there are no mandates requiring water systems to inform their customers of the presence of these chemicals.

Finally, the SDWA authorizes the EPA to require testing of chemicals detected in drinking water for potential hormone disrupting effects, but the EPA has dragged its feet in implementing its endocrine disruptor screening program (EDSP). Since so many pharmaceuticals are potential hormone disruptors, this delay increases the potential risks of drinking water contaminated with these chemicals. Despite the recommendations of its advisory committee to include drinking water contaminants on its list of chemicals intended to be screened in the endocrine disruptor screening program as required by the SDWA, the EPA’s initial list of 73 chemicals to begin screening under the EDSP does not include any chemicals identified as drinking water contaminants, including pharmaceuticals.

Thus, although the SDWA confers sufficiently strong authority on the EPA to address these contaminants, the EPA has not exercised that authority to deal with pharmaceuticals in drinking water.

### **C. DRUG ENFORCEMENT AGENCY (DEA)**

Intentional disposal of pharmaceuticals that are problematic because of their attractiveness to drug abusers and recreational users are regulated by the DEA under the Drug Abuse Prevention and Control Act.<sup>17</sup> DEA regulations exclude individual consumer disposal, however, as long as the disposal is by the prescription holder. Furthermore, and problematically, the DEA specifically prohibits consumers from returning controlled substances to the pharmacies where they originally acquired them, or to other controlled substances registrants such as reverse distributors, except in the case of a recall or a dispensing error. This prohibition has created one of the largest barriers for consumers, hospitals, and other entities to dispose of their unwanted and expired pharmaceuticals by any method other than flushing or trashing.

Because DEA guidelines suggest that it is only appropriate to return pharmaceuticals to the pharmacy in the case of a recall or dispensing error and that there are no other provisions to cover the return of unused or expired pharmaceuticals, it is likely that ordinary citizens, and even health professionals, could logically conclude that the easiest method for disposing of unused pharmaceuticals is by flushing them down the toilet. Later in this report, we discuss in detail some drug disposal programs that have tried to deal with these problems.

## IV. Drug Design

As with many environmental contaminants, addressing the problem of pharmaceuticals in drinking water should start at the very beginning of the pipeline where drugs are designed. We recognize that it is unlikely that environmental impact would ever dominate a decision to develop or license a drug. However, there are some characteristics about many pharmaceuticals that, if appropriately addressed, can have environmental benefits as well.

First, the degree to which pharmaceuticals are metabolized in the body varies greatly. For example, 80-90 percent of the antibiotic amoxicillin is excreted in the parent form, but only three percent of the anti-epileptic drug carbamazepine is excreted unchanged.<sup>1</sup> Approximately 45-62 percent of the drug ciprofloxacin is excreted in human urine, while another 15-25 percent is excreted in the feces.<sup>2</sup> (See Table 6 for other excretion rates, Section VIII.) Even when pharmaceuticals are metabolized to inactive conjugates in the digestive tract, they can nonetheless remain a threat to the environment, since these conjugates are frequently cleaved in wastewater treatment systems and sewers, causing the original active parent compound to be released. These factors are highly relevant to the environmental impacts of using these drugs and could be more rigorously evaluated during the drug design phase to minimize problems without undercutting the drug's efficacy.

Similarly, there is a wide variability in the environmental persistence of drug compounds. Some are known to be extremely persistent, such as carbamazepine and clofibric acid, the metabolite of the cholesterol medication clofibrate.<sup>3</sup> On the other hand, other drugs degrade more readily, for example through photolysis.<sup>4</sup> In fact, a survey of drinking water from treatment facilities and in tap water from 19 U.S. water utilities found that the occurrence of pharmaceuticals in drinking water is not related to the prescription volume of the drug.<sup>5</sup> For example, the anti-cholesterol drug, Lipitor, is the one of the most frequently prescribed drugs in the United States, but was found in only 3 of 19 treatment facilities and none of the finished or tap water samples. However, drugs such as carbamazepine, gemfibrozil, meprobamate, sulfamethoxazole, and trimethoprim, which were not in the top 200 prescribed pharmaceuticals for 2006 or 2007, were among the most frequently detected in drinking water samples. The authors of this study concluded that "prescription information alone is a poor proxy for source water occurrence because it does not take into account the dosage, pharmacokinetics, removal during wastewater treatment, or environmental fate."<sup>6</sup>

Biodegradation has been found to be an important removal mechanism for some drugs, such as ibuprofen, but this pathway is sensitive to temperature and hence is somewhat seasonal.<sup>7</sup> Sorption to sediment is an important mechanism for the attenuation of hydrophobic contaminants in the water column, but partitioning to sediment is not the same as degradation, because the compound remains available to certain organisms at the bottom of the food chain. Appendix C includes a table that provides half-lives for some pharmaceuticals in aquatic environments.

With rigorous adherence to green chemistry principles, drugs could be designed to reduce the amount of pharmaceutical waste being excreted from our bodies. Drugs could also be more carefully designed or dosed to ensure they are metabolized prior to elimination in the urine or feces. According to one industry expert, green chemists are already at work on concepts such as enhancing bioavailability or designing improved delivery of drugs to the tissues where they are needed, thereby decreasing the required total dose for the patient.<sup>8</sup>

Green chemistry concepts could also be used to substantially reduce the inherent hazard of pharmaceuticals to the environment. The efforts would focus either on designing drugs to "self-

destruct” in the environment, or on nonpolluting technologies to decompose APIs and their active byproducts prior to discharge into the environment. Active ingredients that decompose using natural processes relevant to the pathways by which the drugs are discharged, such as oxidation, hydrolysis, or biological pH, would be the most relevant to achieve this goal. The challenge with these designs, of course, is to ensure that the drug retains its pharmaceutical activity during production, delivery to the patient, and consumption or application. For example, if the drug decomposes too quickly at biological pH then it may become inactive in the patient before it has had its desired therapeutic effect. A drug designed to biodegrade under sunlight must be kept in the dark from production through to dosing the patient. These examples are not barriers, but are considerations of which green chemists and engineers are aware.

Finally, personalized medicine, or “pharmacogenetics,” is a promising and developing field in drug design that will reduce waste, over-prescription, and overconsumption of pharmaceuticals by customizing drug and dosage to the individual consumer.<sup>9</sup> This approach will have the advantage of avoiding the prescription of pharmaceuticals to non-responders, and of avoiding over-dosing. Patients will appreciate a medication more if it works without any side effects.

### **Efforts to Address Design**

We did not uncover any efforts by advocacy or other groups promoting green chemistry in the United States to address the drug design phase in the pharmaceutical industry.

## V. DRUG APPROVAL

As mentioned earlier, the FDA approves drugs for the market that are not generally recognized as safe and effective and therefore must be tested to prove their safety and efficacy.<sup>1</sup>

Clinical testing is primarily broken into three phases. During Phase 1 trials, data on drug absorption, distribution, metabolism, and excretion in humans are collected and analyzed to evaluate drug safety, especially short-term side effects.<sup>2</sup> Phases 2 and 3 are focused on efficacy in patients, although safety is continually monitored throughout the whole process. In particular, Phase 3 focuses on efficacy between different patient populations, different doses and in combination with other drugs. In addition, post marketing commitments allow the FDA to continue to track the drug's safety and efficacy after approval. Once approved, the pharmaceutical company formally sends to the FDA a new drug application that includes all clinical trial and animal data and information on how the drug is manufactured and behaves in the body. Notably, most of this process is beyond public scrutiny.

Outside of the NEPA requirements described earlier, the FDA does not explicitly require that environmental impacts be considered for a pharmaceutical to be approved. The FDA does provide some guidance, however, on one category – antibiotics – which dominate the animal drug applications. That guidance “outlines a comprehensive evidence-based approach to preventing antimicrobial resistance that may result from the use of antimicrobial drugs in animals.”<sup>3</sup>

### A. REGULATORY EFFORTS TO ADDRESS PROBLEMS IN DRUG APPROVAL

The FDA is responsible for approving the use of antibiotics for animals. Until recently, the FDA routinely granted approval for use of antibiotics in animal feed for non-therapeutic uses, including antibiotics used extensively to treat human illnesses. The Keep Antibiotics Working (KAW) Coalition's campaign and several of its lead member groups have waged a steady campaign over the past seven years to pressure the FDA to: adopt additional restrictions on the approval of new antibiotics for animal use; reject specific applications for both new uses and off-label uses of antibiotics critical for human use; and to revisit those approvals already granted to determine whether they need to be withdrawn to protect the public.

In 2003, the FDA issued a guidance document intended to specifically address the issue of antibiotic resistance in the consideration of new drug approvals for animal uses. The guidance presented a qualitative methodology for evaluating the risk that new or existing drugs would cause resistance problems of significance for human medicine. Unfortunately, while this guidance has much merit, it is not mandatory or enforceable, and its effectiveness is limited. Importantly, the guidance has not been applied to drugs already on the market, which are a much greater problem than new approvals, since they are ongoing contributors to the evolution of antibiotic resistant diseases.<sup>4</sup> It is in part the FDA's failure to even begin reconsidering existing approvals that has led groups to work on passing legislation to mandate the re-review of existing approvals for non-therapeutic uses of antibiotics used both in human medicine and food animal production.<sup>5</sup>

In April 2005, four public health and environmental groups petitioned the FDA to withdraw approvals for seven classes of antibiotics used as agricultural feed additives for their failure to meet the safety criteria contained in the FDA's guidance on agricultural antibiotics.<sup>6</sup> To date, the FDA has yet to take action on the petition. Following actions in Sweden in 1986 and Denmark in 1998, the European Union issued a ban on the use of growth-promoting antibiotics in food animal production, which took effect in 2006.<sup>7</sup>

Despite the general anti-regulatory climate of the last decade, KAW's members had some successes. In July 2005, the FDA took the important step, after a long campaign by the KAW and some of its key members, of cancelling the approval of Cipro-like antibiotics (the fluoroquinolones) for use in poultry, marking the first time the FDA has withdrawn approval for an agricultural antibiotic due to concerns about antibiotic resistance. One major corporation, Bayer, fought the FDA's action for five years, but ultimately dropped its appeals of the FDA's decision.<sup>8</sup> In July 2008, the FDA banned the use of third and fourth generation antimicrobial cephalosporins for extra label veterinary uses.<sup>9</sup> However, in December the FDA reversed itself and dropped the ban in the face of overwhelming industry opposition.<sup>10</sup>

## **B. LEGISLATIVE EFFORTS ADDRESSING DRUG APPROVAL**

Despite some fleeting successes in the regulatory arena, attention has rightly turned to Congress to develop a more proscriptive approach to FDA approvals. In 2008, the Animal Drug User Fee Amendments were signed into law, which, among other things, require the collection of veterinary drug use data essential to the assessment and management of antimicrobial risks represented by approved antimicrobial drugs.<sup>11</sup> This provision will address the problem of lack of publicly available information on the volumes and uses of antibiotics in animal agriculture, by requiring manufacturers of antimicrobial animal drugs to submit annual reports to the FDA. These reports would include the quantity of each antimicrobial animal drug sold for each kind of food producing animal and the claimed purpose of use for each kind of animal (such as growth promotion, weight gain, feed efficiency, disease prevention, disease control, or disease treatment).

Legislation has been introduced in the House and Senate and is supported primarily by the groups that comprise the KAW campaign including the Food Animal Concerns Trust, the Institute for Agriculture and Trade Policy, the Union of Concerned Scientists, the Humane Society of the United States, and the Environmental Defense Fund. The Preservation of Antibiotics for Medical Treatment Act (PAMTA) amends the FFDCA to withdraw approvals for feed-additive uses of seven specific classes of antibiotics which are also used in human medicine. The bill would generally require the FDA to re-review the existing approvals of animal antibiotics also used in human medicine within two years. The Senate version of the bill authorizes the Secretary of Agriculture to pay poultry and livestock producers to defray the transition costs of reducing the use of antimicrobial animal drugs.

The PAMTA's lead sponsor in the Senate was Senator Kennedy and in the House is Representative Louise Slaughter, who both introduced the bills in 2009. However, opposition from both the pharmaceutical industry and elements of the farming sector continues to be very strong. Moving this kind of legislation through Congress, even with an administration potentially more inclined toward the protection of public health, will be a major undertaking.

## VI. The Production of Pharmaceuticals

The amount and variety of waste created during the manufacture of pharmaceuticals dwarfs the amount of the actual finished product. The amount of waste generated per kilogram of active ingredient produced can range from 200 to 30,000 kilograms. The manufacturing wastes include biological compounds such as fermentation wastes, the solvents left over when active ingredients are extracted from natural sources, and pharmacologically-active reagents such as anti-coagulants and chemotherapeutic agents. Manufacturing wastes also include chemicals such as cleaning agents and disinfectants used to sterilize equipment and extraction solvents used to isolate and purify active ingredients. The composition of pharmaceutical waste is estimated to be solvents (49 percent), reactants including some biologically-active components (nine percent), water (28 percent), and others (14 percent).<sup>1</sup>

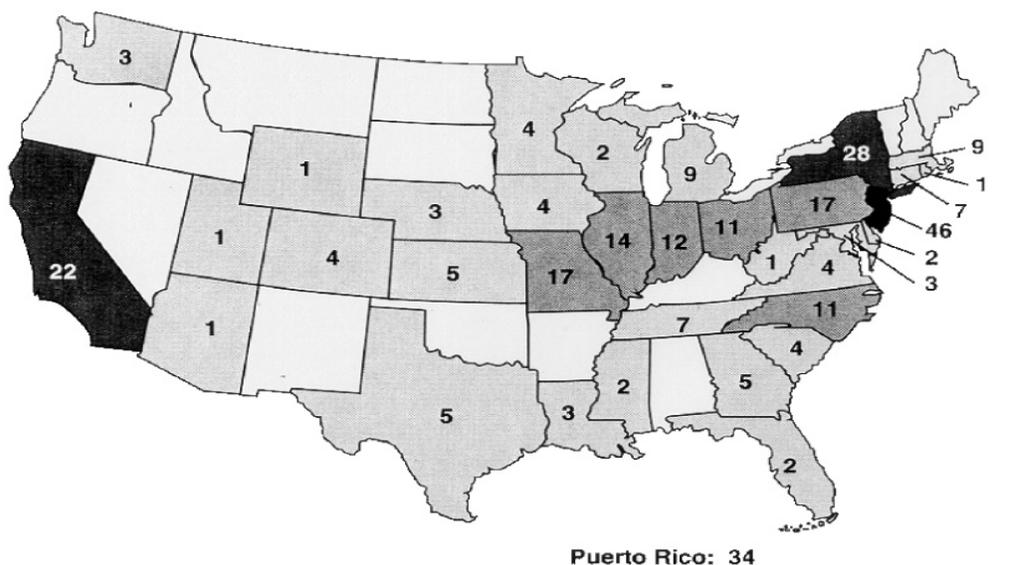
The EPA released a report of the pharmaceutical manufacturing industry ten years ago, documenting releases of many industrial chemicals. (See Table 5, below, for a compilation of the data that the EPA gathered.) However, the Agency did not report on releases of drug products, metabolites, or biologically-active by-products unique to this industry.

**Table 5. EPA Compilation of Toxic Releases Inventory Reported Discharges from Pharmaceutical Manufacturing Facilities (1987, 1994)<sup>2</sup>**

Compound	Total Annual Discharge 1987 (lbs)	Total Annual Discharge 1994 (lbs)	Change
Benzene	136,600	46,116	-66 %
Carbon Tetrachloride	125,982	1,710	-99 %
Chloroform	664,456	336,587	-49 %
Methyl isobutyl ketone	2,918,922	960,365	-67 %
Methyl cellusolve	77,887	12,990	-83 %
Methylene chloride	25,262,249	9,071,052	-64 %
Phenol	73,502	54,360	-26 %
Pyridine	216,100	75,280	-65 %
Xylene	1,469,212	492,394	-66 %

The location of pharmaceutical manufacturing facilities by state is provided in the map. (See Figure 2.) Notably, of 304 facilities, over 15% are located in New Jersey, and over 10% are in Puerto Rico, with New York and California running third and fourth.<sup>3</sup>

**Figure 2 Locations of Pharmaceutical Manufacturing Facilities.**



These states with the greatest concentrations of pharmaceutical manufacturing plants are most at risk of contamination from this source. In fact, the AP recently found that at least 271 million pounds of pharmaceuticals are entering the waterways that often provide drinking water.<sup>4</sup> We suspect, however, that industrial manufacturing is not a priority source of API contamination throughout the entire United States because it is mainly localized to just a few states, with the bulk of manufacturing done overseas. Rather, the highest impacts are likely to be immediately downstream of factories. With the exception of Puerto Rico, most pharmaceutical manufacturing occurs outside of the United States, predominantly in Ireland, Mexico, Singapore, China, India, and South America.<sup>5</sup>

We were unable to find information concerning how much of the environmental pharmaceutical load to the environment is coming from manufacturing facilities and whether or not the regulations effectively keep them out of the water. However, it seems unlikely to us that manufacturing facilities are as large a source of contamination nationally as the other sources discussed in this report.

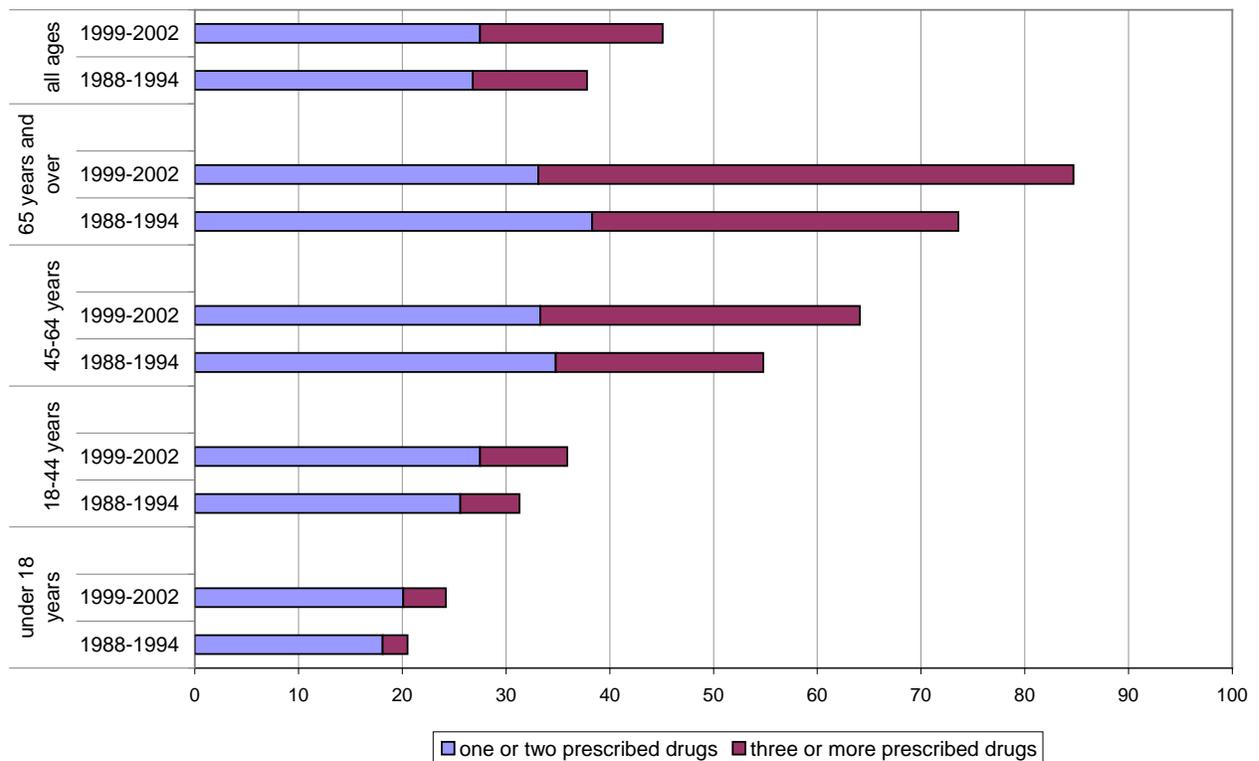
### **Efforts to Address Production**

Efforts to address the environmental impact of the production of pharmaceuticals should include green chemistry concepts – as discussed earlier. Designing pharmaceuticals so that the same therapeutic effect can be achieved using less API is an important goal of green chemists; by increasing the efficacy of a drug formulation, it is possible to decrease the amount of drug that must be manufactured, thereby decreasing production waste significantly, and also the amount of drug in the dose.<sup>6</sup> Some pharmaceutical companies and green chemists are also gaining some ground on reducing the use of water in the production process and reducing the use of hazardous solvents.<sup>7</sup> However, we did not uncover any efforts by advocacy or other groups targeting the production phase of the pharmaceutical industry.

## VII. Overuse of Pharmaceuticals

Pharmaceutical consumption has increased significantly over the past two decades, leading to increased loading of pharmaceutical discharge and waste into the environment. Every month, for example, 135 million people use prescription medicines with a total of four billion prescriptions given out each year.<sup>1</sup> The National Health and Nutrition Examination Survey data show that the percentage of Americans who reported using prescription medication (during the previous month) increased from 39 percent to 44 percent between 1988 and 2002. During the same period, the percentage of persons who reported using three or more prescription drugs in the past month increased from 12 percent to 17 percent of the population. Ninety percent of seniors use at least one medication. Even more striking is the increase in the percentage of older persons who reported taking three or more prescribed medications during a one-month period—almost half of those 65 and over between 1999 and 2000, compared with just over one-third 15 years ago (1988-1994). (See Figure 3.)

**Figure 3. Percent of Persons Reporting Prescription Drug Use in the Past Month, by Age<sup>2</sup>**



At the same time that the pharmaceutical industry reaps profits from large sales, the rising costs of health care, along with employers limiting their portion of health care coverage, has meant that consumers are paying more in real dollars at the pharmacy than ever before. Whereas prescriptions represented only 10.5 percent of total healthcare costs in the United States in 2002, they amounted to 23 percent of out-of-pocket costs for the consumers. Americans spent \$162.4 billion on prescription drugs in 2002, up from less than \$100 billion a decade earlier. This increase is not due

simply to an increase in population; an analysis by the Kaiser Family Foundation attributes the rising costs of prescription drugs to an increasing number of prescriptions, increasing prescription prices, and increasing sales of high-priced brand name drugs.<sup>3</sup>

In addition to the use of prescription medications, over-the-counter medications are readily available, relatively inexpensive, and can be taken in combination with prescription medications, often without the knowledge of the patient's health care providers. It is common for people to self-medicate with over-the-counter medications for ailments such as mild pain and headaches, colds and allergy symptoms, and gastro-intestinal upset. The overuse of over-the-counter medications can not only be risky for a patient's health but can also increase the amount of pharmaceuticals entering the environment. However, there is no data available on the contribution of these medications to environmental contamination, or their disposal patterns. One could assume that most people will dispose of both prescription and non-prescription medications in the same way.

The overuse of medications is driven by a number of complex and interrelated factors, including physician practice, patient expectations and demands, aggressive marketing by pharmaceutical companies, and prescription plan requirements. There is currently no way to tease apart which factor is most to blame for the over-prescribing and overuse of medications.

The problem of overuse is the root cause of a significant percentage of avoidable pharmaceutical contamination in the environment. Furthermore, there are ways to ameliorate the problem and various groups that are addressing it.

## **A. CONTRIBUTORS TO OVERUSE**

### **1. Physician Behavior: Over-Prescriptions**

Over-prescription of medications due to over-diagnosis or misdiagnosis has been documented as part of the problem of the overuse of medications. Physicians with limited time to diagnose and treat patients may be quick to write prescriptions for patients who expect that their ailments can be cured with a quick fix from a pill. Although we were unable to find specific references that quantify the severity of this problem, we present here some examples that have been studied and published in the scientific literature that are illustrative of the problem.

Antibiotics are a class of drugs that are notoriously over-prescribed based on over-diagnosis or misdiagnosis. For example, children are often prescribed antibiotics for a sore throat without having the proper diagnostic test to determine whether or not the cause is bacterial. A 2005 study of Harvard affiliated hospitals found that despite clear guidelines, 53 percent of physicians prescribed antibiotics for sore throats when the actual rates of bacterial infection causing sore throat in children are 15-36 percent.<sup>4</sup> Likewise, in a national survey of adults, 73 percent with sore throats were treated with antibiotics when the expected prevalence of infection requiring antibiotic treatment was only 5-17 percent.<sup>5</sup>

Over-prescribing of medications is not a problem unique to the United States. A 2004 survey of general practitioners in the United Kingdom found that more than 80 percent of practitioners surveyed reported over-prescribing anti-depressants to their patients.<sup>6</sup> The poll by Norwich Union Healthcare also reported that 72 percent of doctors said they were prescribing more anti-depressants than they did five years earlier, many citing a lack of alternatives such as social care or therapy as the reason for the change in their prescribing practices.<sup>7</sup>

## **2. Marketing Techniques Used By The Pharmaceutical Industry**

Another root cause of increasing prescription use is advertising.<sup>8</sup> Manufacturers spent \$25.3 billion on advertising in 2003, with \$22.1 billion (87 percent) directed toward physicians (including \$16.4 billion for the retail value of drug samples), and \$3.2 billion (13 percent) directed toward consumers. Spending for direct-to-consumer (DTC) advertising – typically to advertise newer, higher-priced drugs – was more than eight times greater in 2003 than in 1995.<sup>9</sup>

Aggressive and misleading marketing techniques by pharmaceutical companies have been described in a number of recently published books.<sup>10</sup> They include the medicalization of human conditions and behavior (where “normal” life events become maladies that can be cured by medications), promotion of off-label use of medications, the hiring of physicians to promote pharmaceuticals through publications, and presentations that have been prepared by the drug companies.<sup>11</sup>

For example, incontinence is a real medical condition that varies in severity and is treatable with conservative measures such as pelvic floor exercises. However, through aggressive physician education, a new type of incontinence – “overactive bladder” – was created as a real medical condition requiring drug therapy. Aggressive marketing of the urological medication Detrol was promoted as the way to treat this disease. Detrol is now one of the best selling drugs in the nation (60th in 2007, with sales of over \$600 million).<sup>12</sup> Other examples of “new diseases” that have been promoted to increase drug sales include generalized anxiety disorder, premenstrual dysphoric disorder, and hair loss.

Diseases that once carried a stigma, such as depression or bipolar disorder, are now more readily accepted in society and are being increasingly diagnosed and treated with medications. In addition, obesity and a number of common and related health problems including glucose intolerance (pre-diabetes), high blood pressure, and high cholesterol associated with lifestyle factors such as poor diet and lack of exercise are now readily treated with medications, even though they can be addressed by lifestyle changes that do not require pharmaceuticals.

Three other marketing techniques used by the pharmaceutical industry also raise concerns. First, companies are cleverly misleading consumers about the actual effectiveness of the drugs they advertise. For some of the biggest blockbuster drugs, statements of efficacy misrepresent the actual results from clinical trials.<sup>13</sup> Second, companies have begun using academics as industrial consultants to recommend that young children be prescribed drugs that would commonly be prescribed to adults – such as statins to lower cholesterol or anti-depressants.<sup>14</sup> Third, records of doctors’ prescribing habits are being sold to companies so that drug representatives may tailor their marketing, messages, gifts, and other inducements to individual doctors.<sup>15</sup>

## **3. Off-Label Use**

The off-label use of prescriptions is similarly problematic, often leading to unnecessary and undesirable expanded uses of medication. FDA approvals are for specific medical conditions based on both published and unpublished clinical trial information supplied by the pharmaceutical manufacturer. However, once the FDA approves a drug for prescription use, any physician can legally prescribe the drug for any condition they see fit. For example, a drug might be approved to treat colon cancer but be prescribed by a physician for use in a patient with pancreatic cancer. In some instances, off-label use of a drug may be medically appropriate to treat a problem which has not otherwise responded to an FDA-approved drug. Other medically appropriate off-label uses may occur in pregnant or pediatric patients because drugs typically are not tested in those patient populations. However, the danger in off-label use of medications is that there is often insufficient

evidence to support the safety or efficacy of the drug. And in many instances, there are approved alternatives available that could be safer and more effective.

The off-label use of medications is very common. A 2001 survey of U.S. office-based physicians found that 21 percent of all estimated uses for commonly prescribed medications were off-label, and less than one-third of uses were supported by strong scientific evidence.<sup>16</sup> The frequency of off-label use varied widely among specific medications and drug classes, exceeding 50 percent for some anticonvulsants, psychiatric medications, and anti-asthmatics. In 1996, the GAO testified before the U.S. Congress that one-third of all drug administrations to cancer patients were off-label and more than half of cancer patients received at least one drug for an off-label indication.<sup>17</sup> A recent draft guidance from the FDA relaxes the strict standards for promoting unapproved uses by condoning the distribution of scientific articles describing off-label use. This threatens to increase the promotion of off-label use of medications and reduce pharmaceutical companies' incentive to conduct more detailed research on safety and efficacy.<sup>18</sup>

#### **4. Prescription Plans**

Prescription plans that require distribution of a minimum number of pills could contribute to the accumulation of unused medication being dumped into the environment. For example, to lower costs, many seniors rely on mail order pharmacies for their prescriptions, which require and instruct their customers to ask for 90-day prescriptions instead of 30-day prescriptions. Therefore, because patients change doses of medications for chronic health conditions, they are left with unused pharmaceuticals that need to be disposed of properly. However, we were unable to find evidence that this practice substantially contributes to the problem of pharmaceutical waste.

### **B. EFFORTS TO ADDRESS OVERUSE OF PHARMACEUTICALS**

The over-prescription of pharmaceuticals is a significant issue with which health professionals and practitioners constantly struggle. Therefore, adding a new dimension to the issue—that is, the environmental impacts of the discharge and disposal of these unneeded drugs, or their impacts on non-target populations exposed at levels far below the effective dose—is not likely to further motivate the medical community to address the problem. The development of antibiotic-resistant bacteria, for example, which is such an urgent threat to public health, is much more likely to engage the interest of politicians and the public. Regardless, current efforts to address the overuse of pharmaceuticals, as described below, can still reap environmental benefits.

#### **1. Education and Outreach**

A major solution proposed for the problem of physicians over-prescribing medications because of misdiagnosis or over-diagnosis is outreach and education from professional medical societies. There has been a concerted national effort to educate physicians and the public about the misuse of antibiotics, largely driven by the development of antibiotic-resistant strains of bacteria. The CDC has a Campaign to Prevent Antimicrobial Resistance in Healthcare Settings and a “Get Smart” campaign to educate community members about the proper use of antibiotics.<sup>19,20</sup> Health care organizations such as the Mayo Clinic and Kaiser Permanente also have information on their websites for their members about the proper use of antibiotics.<sup>21,22</sup> Noticeably absent from this advocacy work is the American Academy of Pediatrics, whose only guidance on antibiotics deals with acute ear infections and agricultural use of antibiotics in large animal feeding operations.<sup>23</sup>

Based on information published in the scientific literature, it appears that efforts by professional and public health organizations have been successful in reducing the number of antibiotic prescriptions. In the United States, antibiotic prescriptions for respiratory infections in children less than 15 years

of age fell between 1989-1990 and 1999-2000.<sup>24</sup> Similarly, in England, the number of antibiotic prescriptions issued by family practitioners decreased by 25 percent between 1995 and 2000, from 49.4 to 36.9 million prescriptions (reflecting a fall from 1 to 0.75 antibiotic prescriptions per person per year).<sup>25</sup> Because of the overlapping messages that physicians and other healthcare providers receive from multiple sources, it is not possible to determine which organization has been most effective; however, government support of these efforts has been crucial for their success.<sup>26</sup>

To assess specifically the effectiveness of these educational programs, follow up surveys can be issued to see how physician prescribing practices have changed.<sup>27</sup> While there have been some studies looking at the efficacy of specific programs for antibiotic prescribing practices, no one has conducted a systematic look at the whole practice.

## 2. Influencing Medication Selections Based on Environmental Impacts – the European experience

In 2005, Sweden began a major initiative to classify environmental risk and hazard characterization for every pharmaceutical sold in the country.<sup>28</sup> Using information that pharmaceutical manufacturers already must submit to the Medical Products Agency in Sweden, a producer identifies a level of risk and hazard for each of its products. The hazard assessment is expressed on terms of how persistent, bioaccumulative, and toxic (PBT) the pharmaceutical is once released into the environment (whether by excretion or by disposal). The risk classification is expressed as the ratio of the “predicted environmental concentration” to the “predicted no effect concentration.” Then an independent consulting firm audits that data and either approves or disapproves the risk and hazard assessment. Once approved, the classifications are listed on the publicly-available LIF (Läkemedelsindustriföreningen - the Swedish Association of the Pharmaceutical Industry) website.<sup>29</sup> The group is now starting to determine how to include environmental impacts of production into this classification system.<sup>30</sup>

Figure 4: Example of Data on Pharmaceuticals Extracted from LIF Website

The screenshot shows the Janusinfo Stockholm County Council website. The page title is "Environmentally classified pharmaceuticals" with a last update date of 2009-05-19. Under the heading "R Respiratory system", there is a table with the following columns: Substance, Risk, PBT, P, B, T, Volume in DDD, and ATC. The table lists several substances including ipratropium, budesonide, oxymetazoline, mometasone, levocabastine, and sodium.

Substance	Risk	PBT	P	B	T	Volume in DDD	ATC
<b>Nasal preparations</b>							<b>R01</b>
ipratropium	insignificant	5 N.B.	3	0	2 N.B.	1 320 279	R01A X03, R03B B01
budesonide	insignificant	8	3	3	2	11 074 776 C, E 5 256 990	R01A D05 R03A K07 R03B A02 A07E A06
oxymetazoline	cannot be excl	5 N.B.	3 N.B.	0	2 N.B.	6 710 175	R01A X03, R01A A05
mometasone	cannot be excl	9 obs!	3	3	3 obs!	6 536 335 E 5 745 400	R01A D09 R03B A07 D07A C13
levocabastine	insignificant	5	3	0	2	314 063	R01A C02
sodium	cannot	3	3	0	0	270 704	R01A C01

Groups that participated in this work included the LIF, the Stockholm County Council (the body that ensures that Stockholm residents have access to healthcare and public transit) and other Swedish county councils, Apoteket (the state-run pharmacy chain), and other stakeholders. In fact, six major pharmaceutical companies headquartered either in Europe or the United States (Merck, Lilly, Pfizer, Glaxo, Roche, and AstraZeneca) all approved the use of their data for this classification system.

The creation of this classification system was motivated by the desire to address the effects of pharmaceuticals on the environment. Specifically, when physicians (and to a lesser extent patients) have access to data about the relative risk and hazard associated with multiple medication choices, they will recognize that for a given condition or disease there are choices that are more environmentally responsible. As a result, choosing the less environmentally risky and hazardous pharmaceutical will create incentives for industry to manufacture products that have lower environmental impacts.

To date, every company that sells pharmaceuticals in Sweden has joined this classification system. The cost of the data collection is borne by the company and the cost of the auditor is paid by the LIF (which is also industry-funded). For the most part, the cost has been moderate, mainly because the companies have already collected these data for other purposes. Research on the success of this program is only now beginning.<sup>31</sup>

The desire to spread this system to the European Union has been met with some success. Both the Germans and the Dutch are very involved with conducting these risk and hazard assessments for pharmaceuticals.<sup>32</sup> In addition, the European Medicines Agency is considering including environmental data on the safety labels that are provided on pharmaceuticals.<sup>33</sup> The work being done by these countries to evaluate all of the major pharmaceuticals that are used here provide a readily available resource for us to adapt in the United States.

### **3. Litigation**

The Community Catalyst's Prescription Access Litigation Project uses class action litigation and public education to make prescription drug prices more affordable for consumers by challenging illegal pricing tactics and deceptive marketing by drug companies, pharmacy benefit managers, and other pharmaceutical industry players.<sup>34</sup> These lawsuits are intended to motivate industry to change its behavior so that they will stop, for example, marketing unproven off-label uses and misleading physicians about the efficacy of their drugs.

Pharmaceutical companies have been repeatedly fined for aggressively marketing the off-label use of their drugs to physicians, even after the FDA has explicitly denied the off-label use that is being promoted. Most recently, Pfizer was fined a record \$2.3 billion dollars for their illegal tactics to convince physicians to prescribe drugs such as the anti-inflammatory drug, Bextra, after the FDA denied a request for the off-label uses that were being promoted.<sup>35</sup> Pfizer had previously been fined for illegal marketing of drugs but these cases had not changed corporate behavior. Other pharmaceutical companies have been fined for similar tactics.

### **4. Legislative/Policy**

The Community Catalyst's Prescription Project uses policy changes among academic medical centers, professional medical societies and public and private payers, as well as state and national level policy solutions to eliminate conflicts of interest created by industry marketing.<sup>36</sup> Some of the state and federal policy initiatives involve marketing, consulting, research, speaking, gifts, and meals paid for by industry. States such as Massachusetts, Minnesota, Washington, Colorado, Vermont,

Nevada, Maine, and New Hampshire have introduced gift bans or transparency bills.<sup>37</sup> At the federal level, Community Catalyst has been working on H.R. 5605 Physician Payments Sunshine Act of 2008 (Fazio), which will amend title XI of the Social Security Act to provide for transparency in the relationship between physicians and manufacturers of drugs, devices, or medical supplies for which payment is made under Medicare, Medicaid, or SCHIP, and for other purposes.<sup>38</sup>

## **5. Private Sector**

The Long Term Care Pharmacy Alliance conducts regular safety reviews to determine if any changes are needed in long term care patients' medications and dispense of drugs in specialized packaging systems that reduce the possibility of medication errors.<sup>39</sup>

## **6. Evidence-Based Prescribing Practices**

Physicians who practice evidence-based prescribing choose a medical treatment based on the efficacy and cost-effectiveness of treatment options, the benefits or harms of a treatment, and consider the patient's own involvement in the treatment plan. This method of prescribing is free from the marketing messages that often influence physicians' prescribing patterns. Evidence-based prescribing can include both on and off-label prescriptions. When put into practice, evidence-based prescribing could help with the over-prescribing problem, resulting in fewer unused medications. One model to promote evidence-based prescribing practices that could be replicated in other states is the Drug Effectiveness Review Project. This project provides systematic evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes to inform public policy and related activities.<sup>40</sup> Additionally, the Federation of State Medical Boards has recently launched a new web-based tool for educating physicians about pharmaceuticals.<sup>41</sup> The portal, called the "Online Prescriber Education Network," offers free continuing medical education credits to physicians and provides free access to unbiased sources of information about drugs. This project was funded by a 2004 consumer protection settlement with Warner Lambert, a division of Pfizer, over allegations of deceptive off-label marketing of the drug, Neurontin. Another resource for physicians is Smartprescribe.org, an on-line curriculum from Wake Forest University designed to educate physicians about how to assess information from pharmaceutical companies. Similarly, physicians can refer to PharmedOut, an independent, publicly funded project that empowers physicians to identify and counter inappropriate pharmaceutical promotion practices, promotes evidence-based medicine by providing news, resources, and links to pharmaceutical-free continuing medical education courses.<sup>42</sup>

## **7. Congressional Oversight**

Representatives Dingell and Stupak held a hearing in 2008 on direct-to-consumer advertising and celebrity endorsements of drugs.<sup>43</sup> Also in 2008, Senator Grassley investigated industry funding of professional organizations such as the American Psychiatric Association. Additionally, Representative Dingell and Senator Grassley are working together to give the FDA broad powers to levy fines, order drug recalls, and restrict drug-industry advertising.<sup>44</sup>

## VIII. Pharmaceuticals Entering the Waste Stream

Once a pharmaceutical is prescribed to a patient, fed to livestock, or applied to a family pet, little attention is paid to what happens afterwards. The pathway for the pharmaceuticals entering the waste stream can be characterized as either unintentional or intentional. “Unintentional releases” refers to the excretion of both metabolized and unmetabolized pharmaceuticals from animals or humans. “Intentional releases,” on the other hand, refers to the disposal of unused or expired pharmaceuticals by flushing down the toilet, rinsing down the sink, or throwing into the trash.

Even within these categories, there are major differences. For example, pharmaceuticals unintentionally released by humans are usually excreted into a sewer system, which treats the contaminants to some extent with various techniques prior to discharge. On the other hand, pharmaceuticals used in aquaculture and agriculture are often discharged directly into the water or soil without treatment.<sup>1</sup>

### A. INTENTIONAL RELEASES

Unfortunately, reliable and adequately detailed data on both the volume of sales, human consumption, and disposal of pharmaceutical products is not publicly available. Estimates have therefore been pieced together from small studies, surveys, and the claims of industry trade groups that cannot be independently verified. The failure of the industry and its trade groups to provide detailed and independently-verifiable market data prevents regulators, the public, and Congress from making informed decisions on how best to reduce pharmaceutical contamination. Nonetheless, the authors of this report understand these limitations and here attempt to provide a summary of what is considered to be the best publicly-available data at this time.

#### 1. Disposal Habits of the General Population

Because there are no official government or private records on pharmaceutical use and disposal, data on disposal practices and the reasons for unused medications have been collected by take-back programs or regional surveys. In California, data from an unused medication collection program suggests that 52 percent of over-the-counter (OTC) medicines are discarded unused, compared to 45 percent of prescription medicines.<sup>2</sup> Interestingly, the program administrators found that the vast majority of the medicines (72 percent) were returned because they were expired or outdated, suggesting that most doctors are either over-prescribing drugs or that patients are simply reluctant to finish their prescriptions.<sup>3</sup> A collection program in Maine attributed prescription changes or medication that is no longer needed as the reasons more than half of the waste was generated.<sup>4</sup> Research by the Teleosis Institute shows that 40 percent of waste is due to drug interactions, allergies, or side effects.<sup>5</sup>

Failure to finish prescriptions is likely a common problem and contributor to pharmaceutical waste. Another U.S. study found that only two percent of people finish their prescriptions.<sup>6</sup> A very high percentage of drugs – as much as 50 percent of many prescriptions and 80 percent of antibiotics – are said to go unused.<sup>7</sup> The industry trade group PhRMA disagrees, estimating that only about three percent of all medicines go unused.<sup>8</sup>

A 1996 U.S. survey of 500 callers to a poison information center found that the most common methods of disposal of unused medications were trash disposal (54 percent), flushing down the toilet or rinsing down the sink (35 percent) and simply not disposing (seven percent). Only 1.4

percent of respondents reported returning expired medications to a pharmacy.<sup>9</sup> More recently, a 2006 survey of pharmacy customers in Tacoma, Washington found that more than half of the respondents reported storing prescriptions in their homes (54 percent) and flushing them down the toilet (35 percent).<sup>10</sup> Only 22.9 percent reported returning the prescriptions to a pharmacy. A survey of southern California residents showed a similar trend with 45 percent disposing of their pharmaceuticals in the trash and 28 percent disposing of them down the toilet or sink. And finally, a random survey in King County, Washington showed that 52 percent of respondents disposed pharmaceuticals in the trash, 20 percent flushed them down the toilet or sink, and only one percent returned them to a pharmacy or doctor.<sup>11</sup>

In contrast, a British survey of 400 households published in 2005 reported that 52.8 percent of respondents finish their medication and thus have no leftover to dispose.<sup>12</sup> Of those that are disposed, 63.2 percent of respondents discarded them in household waste, 21.8 percent returned them to a pharmacist and 11.5 percent emptied them into the sink or toilet. A small number took them to municipal waste sites that sometimes have special waste facilities. When broken down by drug type, nearly 80 percent of people reported consuming all of their painkillers, whereas only 18 percent of respondents reported finishing antibiotics, 50 percent finished antidepressants, and 50 percent finished beta-blockers.<sup>13</sup> It should be noted that the legal framework governing the pharmaceutical returns is not as tight in England as it is in the United States and therefore take-back programs are more prevalent and simple. However, general practice even with more prevalent take-back programs is to flush unused pharmaceuticals.<sup>14</sup>

## **2. Unused Waste from Deceased Population**

Ruhoy and Daughton (2007) devised a rather unique and robust study designed to characterize and quantify drugs left after people die.<sup>15</sup> They analyzed data collected over 13 months, which included an average of three APIs per decedent. Inhalers, patches, and syringes were not included in this study. The authors reported that over 92 percent of medications found at the site of death were flushed, seven percent were disposed of in household trash, and less than one percent were incinerated by law enforcement services.<sup>16</sup>

Ruhoy and Daughton also presented a more complete analysis of the leftover drugs from the deceased population.<sup>17</sup> They provided data on the type and amount of drugs reported by coroner's offices from the deceased population whose deaths were documented by a coroner. Since this population represents about 11 percent of deaths across the country, multiplying by a factor of nine provided an estimate for the deceased population nationwide.<sup>18</sup> Based on these assumptions, the amount of pharmaceutical waste coming just from the nation's deceased population into the sewage treatment systems would increase concentrations of water entering sewage treatment systems from drains (toilets and sinks) by 2.4 parts per million, assuming average sewage flow rates.<sup>19</sup>

## **3. Institutional Facilities**

In addition to hospitals, long term care facilities (LTCF) and other institutions also deal with large quantities of unused pharmaceuticals.<sup>20</sup> These facilities, including assisted living facilities, nursing homes, coroners, hospice, veterinary practices, dental offices, public housing, schools, daycare, correctional facilities, cruise ships, pet keepers, and hobby farms, have to deal with issues separate from households and hospitals. For example, nursing home residents are transient (they change homes, facilities, move to hospice or pass away), and to avoid liability issues, most facilities will not transfer medications. Therefore, these facilities are left with large quantities of unused medications. For the most part, the protocol for these types of facilities is to flush.<sup>21</sup>

There is little information about the extent to which these facilities contribute to the pharmaceuticals in the waste stream problem. Some estimate that 20 to 30 percent of pharmaceuticals disposed into the waste stream may be coming from these groups.<sup>22</sup> One survey in Washington State found that over 65 percent of pharmaceutical waste was coming from “specialty outpatient” facilities, over 20 percent from hospitals, and about five percent coming from nursing homes, boarding homes, and retail pharmacies.<sup>23</sup>

A significant barrier to ensuring responsible disposal of pharmaceuticals is that very few medical professionals, including doctors, nurses, pharmacists, or administrators, understand all the issues related to disposal. They are not taught the consequences of various disposal methods nor do they have any training in RCRA or other legal requirements that govern disposal of some pharmaceutical products when generated in large enough quantities. In fact, there is little, if any, teaching of proper disposal of pharmaceuticals, or legal requirements in medical and dental, nursing, pharmacy, or veterinary schools. This lack of knowledge coupled with historically low rates of enforcement of RCRA (or state) violations have led to widespread lack of compliance with the statutory requirements.<sup>24</sup> Recent enforcement initiatives by a few EPA regions like Region 2 and states like California and Indiana have highlighted the extent of lack of compliance and lack of knowledge of the statutory requirements.<sup>25</sup> These initiatives have also reportedly generated a great deal of attention in the industry to getting technical assistance and moving toward compliance.<sup>26</sup>

Even in the absence of convincing data about the adverse environmental and human health effects of these contaminants, public safety considerations motivate otherwise unmovable decision-makers. Inappropriate or inadequate disposal of unused or expired pharmaceuticals can lead to accidental poisonings, intentional drug abuse, or theft and resale. Both nationally and internationally, medications are the most common poison exposure category.<sup>27</sup> Senior citizens – the largest consumers of prescribed medication – are particularly vulnerable because of their tendency to self-prescribe medicines to treat new, undiagnosed symptoms.<sup>28</sup> In addition to these risks, medicines that are not consumed represent wasted health care dollars, which drive policymakers to address the accumulation of unused and expired drugs.

## **B. UNINTENTIONAL RELEASES**

### **1. Agriculture**

Confined animal feeding operations (CAFOs; also known as “factory farms”) are large-scale producers of hogs, poultry, beef or dairy cows – typically housing from thousands to tens of thousands or even hundreds of thousands of animals. These facilities produce enormous amounts of waste, which pose significant challenges for storage and disposal. Hog waste, for example, is typically stored in open lagoons, roughly the size of football fields. Drier animal waste, such as “chicken litter,” is stored in piles, often outside where rain can lead to runoff into nearby waters. After being stored, animal waste is typically spread on surrounding crop fields as fertilizer for crops. These “spray fields,” as well as the lagoons and litter piles, are sources of pollution that can introduce antibiotics, hormones, and other contaminants into our waterways.

Waste lagoons repeatedly discharge pollution into the nation’s waters through “over-topping,” failure, and leaking into groundwater.<sup>29</sup> Animal waste also reaches waterways when it runs off spray fields.<sup>30</sup> Although a certain amount of waste can be sprayed onto surrounding fields as fertilizer, crops can only take up so much nitrogen or phosphorus before they are “full.” The waste that is not taken up by plants remains available in the soil and can run off of the fields into nearby streams or other waters during wet weather. Because CAFOs produce such enormous amounts of waste and have relatively few disposal fields close by, they commonly apply waste in excess of the optimal

amount to fertilize crops, over-saturating the soil and sending waste into waterways bordering the spray fields. It is primarily from these sources – storage lagoons and spray fields – that animal waste pollutes our waters.<sup>31</sup>

In agriculture, the pharmaceutical contaminants of greatest concern are antibiotics, because of their contribution to the growing problem of antibiotic-resistant pathogens. Tens of millions of pounds of antibiotics are used in agriculture to treat infections, to compensate for conditions that contribute to infection, and to promote growth (as feed additives). Many of these antibiotics are in the same classes of drugs that are used in humans.<sup>32</sup>

Troubling estimates are that nearly two trillion pounds of animal wastes are produced annually in the United States and that between 25-75 percent of antibiotics are excreted unchanged in feces and can persist in the soil after land application.<sup>33,34</sup> Subsequently, a large amount of antibiotics (and antibiotic-resistant bacteria) are entering waterways through groundwater contamination, overflow of waste lagoons into surface water, or by over-application of manure as fertilizer in farm fields. A recently published study found evidence of fecal contamination and increased levels of antibiotic-resistant bacteria downstream of a swine concentrated feeding operation.<sup>35</sup> Other studies have found antibiotic-resistant bacteria in groundwater underlying a swine waste lagoon.<sup>36</sup> As such, the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in humans. As mentioned before, antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists agree that the long-term exposures to low levels of antibiotics common in both growth promotion and disease prevention promote bacterial resistance by exerting selective pressure for genes that allow microorganisms to withstand the effects of antibiotics. It is unknown whether, or to what extent, the low levels of antibiotics currently found in drinking water can select for resistant bacteria.

As concern about the growing phenomenon of antibiotic-resistant bacteria grows, the large-scale use of antibiotics for non-therapeutic uses is receiving greater scrutiny. As noted earlier, there are differing estimates of the proportion of total antibiotics used in the agricultural sector. Regardless of which estimates are correct, the contribution of the problem from CAFOs is high. In fact, the European Union has banned non-therapeutic agricultural use of antimicrobials that are important in human medicine and has banned feeding of antibiotics for growth purposes.<sup>37</sup> Notably, the National Research Council estimated that the average annual cost per capita to consumers of a total ban on all antibiotic use ranged from \$4.84 to \$9.72. The nominal impact on prices ranged from \$0.013 to \$0.026 per pound for poultry to \$0.03 to \$0.06 per pound for pork and beef.<sup>38</sup>

As discussed earlier, CAFOs also make widespread use of steroids and have been found to have detectable concentrations of a sex hormone mimic in their discharge.<sup>39</sup>

## 2. Human Excretion

It is possible to estimate through modeling the amount of API that enters the environment through excretion by incorporating usage data with knowledge about the amount of active ingredient that is excreted and the known effectiveness of the treatment techniques used by wastewater and municipal drinking water facilities.<sup>40</sup> For example, Table 6 provides the urinary excretion rates of some pharmaceuticals.

**Table 6. Urinary Excretion Rates of Unchanged Active Ingredient for Selected Pharmaceuticals<sup>41</sup>**

Drug	Therapeutic class	Parent compound excreted (%)
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Ibuprofen	Painkiller	10
Paracetamol	Painkiller	4
Amoxicillin	Antibacterial	60
Erythromycin	Antibacterial	25
Sulfamethoxazole	Antibacterial	15
Atenolol	$\beta$ -Blocker	90
Metoprolol	$\beta$ -Blocker	10
Carbamazepine	Antiepileptic	3
Felbamate	Antiepileptic	40–50
Cetirizine	Antihistamine	50
Bezafibrate	Lipid regulator	50

Although it is possible to do modeling based on this information, no one has done studies that have put these models to the test to see if the numbers are accurate. As noted earlier, this is a very important component for establishing effective policy initiatives. Accordingly, there must be calls for immediate efforts to determine the relative source contribution of pharmaceuticals in the environment that comes from human metabolism.

### C. EFFORTS TO ADDRESS IMPROPER DISPOSAL

There is heightened scrutiny on intentional disposal of medications, mainly because of the concern about the potential for accidental poisonings, especially in vulnerable populations such as children and the elderly, the intentional abuse by teenagers or others, and the theft and resale of certain pharmaceuticals.<sup>42</sup> In addition to these dangers, throwing out unused or expired drugs is a huge waste of healthcare money.<sup>43</sup>

For example, a 2006 pilot project by the University of Minnesota Technical Assistance Program found that two different hospitals both lost substantial amounts of money due to waste from over-ordering by the pharmacy, resulting in the medications expiring on the shelf and having to be disposed of as waste. The first hospital was a small community hospital caring primarily for elderly chronically ill patients; the second was a large county hospital with a patient population comprised of acute care and critically ill patients. The project identified the top ten wasted drugs based on cost and frequency at each institution. The small (25 bed) hospital lost about \$35,000 per year (including purchase and disposal costs). The larger hospital lost about \$80,000 per year (comprising 20 percent of their inventory). This pilot project created a model for other healthcare facilities to conduct similar audits and save money. In addition, improved record-keeping with electronic dispensing systems (for example, Pixis systems) could facilitate the inventory process.

Also, an estimated billions of dollars nationally come from waste sample medication. In one physician office, a pilot project found that the retail value of the medications going to waste was \$16,000 (about \$5 per patient). The project instituted a system whereby a patient was given a voucher to take to the pharmacy to pick up a trial dose (for example, five pills). The voucher system was a win-win because it reduced over-prescriptions, reduced expenses for the pharmacy (which was reimbursed by the manufacturers), and reduced disposal costs for the physician's office.

In recognition of these concerns, the Second International Conference on the Environment, held in Athens, Greece, adopted a declaration in 2007 calling on governments, non-governmental organizations, and citizens to combat the six major concerns associated with unused drugs: childhood overdoses, household drug theft, accumulation of drugs by the elderly, environmental

impacts, improper international drug donation, and wasting of healthcare money.<sup>44</sup> Countries whose attendees signed the declaration by vote included the United States, Canada, the United Kingdom, Spain, Romania, Greece, Germany, Switzerland, India, the Philippines, and Italy.<sup>45</sup>

## **1. Regulatory**

U.S. guidelines for the proper disposal of prescription drugs are contradictory and in some cases depend on the type of drug in question. The Office of National Drug Control Policy, for example, identifies certain drugs that should be flushed down the toilet, rather than thrown in the trash (including OxyContin, morphine, and Percocet.)<sup>46</sup> In contrast to the White House, the American Pharmacists Association and the U.S. Fish and Wildlife Service jointly recommend not flushing medications, but rather crushing or dissolving solid medications and mixing with a substance like kitty litter and placing it in a sealed plastic bag.<sup>47</sup>

### **DOD/FDA Shelf Life Extension Project**

In an attempt to prepare for war or other major military contingencies, the Department of Defense (DOD) keeps a large stockpile of “critical medical material” including a number of pharmaceuticals. The DOD has spent an inordinate amount of money replenishing these stockpiles as they hit their expiration date. In an attempt to curb some of this spending they instituted the DOD/FDA shelf-life extension program (SLEP).<sup>48</sup>

When stockpiles are approaching their expiration date, the DOD, or one of the other participating agencies, sends samples of the drugs to the FDA for testing. They undergo “stress testing” and various other tests to determine if the expiration date can be extended. Drugs that pass the SLEP tests are re-labeled accordingly and placed back on the shelf. There is a ten year cap on extensions, but some drugs have been shown to degrade over a smaller time-scale. All the results are kept in an on-line inventory so that different agencies/locations can easily determine which drugs they can extend without further testing.

The program only applies to the stockpiles of drugs and not the entire \$1.2 billion in prescription and OTC drugs that the DOD buys each year. Currently, there are approximately \$87 million worth of stockpiled drugs. The stockpile includes a wide range of pharmaceuticals including broad range antibiotics, atropine automatic injectors, diazepam, and anti-malaria tablets.<sup>49</sup> Recently, the value of extended drugs has been around \$33 million a year with testing costs of \$350,000, a return of nearly 94 to 1. Those drugs that cannot be extended are sent to the Defense Reutilization and Management Office for “proper disposal,” although it is unclear whether that is incineration or landfilling.<sup>50</sup> Extending this program to facilities that keep large stockpiles of pharmaceuticals on hand may be possible. For individual households, however, it would likely be more cost effective to buy new drugs than to have old ones tested for expiration date extension. However, without security clearance to access protected parts of the website, it is difficult to find out more information about the program.

## **2. Legislative and Policy**

Maine has passed legislation to create a pharmaceutical take-back program that is currently being implemented with preliminary results expected to be publicized later in 2009.<sup>51</sup> In addition to the legislation passed in Maine and a similar one pending in Washington, California passed a bill in 2007 to create model take-back programs and provide financial assistance for implementing them.<sup>52</sup> Also, Indiana passed legislation addressing reverse distribution from pharmacies.<sup>53</sup> In fact, there continues to be much legislative activity on this issue around the country.<sup>54</sup>

As recently as July 2008, the Great Lakes and St. Lawrence Cities Initiative passed a resolution addressing pharmaceuticals in the water, motivated in part by current research associating pharmaceuticals with ecological harm and by the lack of regulation on pharmaceutical disposal.<sup>55</sup> The resolution advocates for an increase in pharmaceutical take-back programs and urges federal, state, and provincial governments to update their regulations on current programs. The initiative will conduct its own survey on the effectiveness of collection programs and hopes to form multi-interest working groups to develop more effective take-back programs in the future.

More recently, other municipalities and even the federal government have begun to tackle the issue. For example, the District of Columbia introduced the Unused Safe Pharmaceutical Disposal Act of 2009 and U.S. Representative Miller introduced a bill to push the EPA to convene a task force to examine the issue of proper disposal of pharmaceuticals.

Even more recently, Illinois passed a law that prohibits health facilities from flushing medications down the toilet. Effective January 1, 2010, health care institutions may not discharge, dispose, flush, pour, or empty any unused medication into a public wastewater collection system or septic system.<sup>56</sup> Violators can be fined up to \$500.

### **3. Education and Outreach**

One recent initiative intended to improve medical professionals' understanding about the harm caused by improper disposal of unused pharmaceuticals is the 2006 report by Hospitals for a Healthy Environment and PharmEcology, "Managing Pharmaceutical Waste: A 10-Step Blueprint for Health Care Facilities in the United States," which provides a thorough review of the RCRA, the DEA, and other federal regulations that affect pharmaceutical waste.<sup>57</sup> An update of the Blueprint is underway, as well as a state-specific blueprint for California.

Some groups have set forth guidelines and best management practices for pharmaceutical disposal. For example, the American Veterinary Medical Association approved in July 2009 best management practices for minimizing unused pharmaceuticals, encouraging incineration of pharmaceuticals, and educating clients on proper disposal.<sup>58</sup>

### **4. Private Sector**

Providing access to appropriate methods for safe disposal of accumulated unused or expired pharmaceuticals not only addresses environmental concerns, but also attacks other serious public health concerns with the use and abuse of pharmaceuticals.

The Product Stewardship Institute (PSI) has a project that focuses on the disposal of unwanted or waste medications from households, long term care facilities, and other sources.<sup>59</sup> The project will evaluate the need for a nationally coordinated system for the management of unwanted/waste pharmaceuticals that allows for multiple solutions that reflect local and regional differences. The project seeks to increase the safe, legal and environmentally protective management, collection and disposal of unwanted and waste pharmaceuticals through the development of best management practices. In December 2008, the PSI held a second national dialogue on these issues.<sup>60</sup>

#### ***a) Hospitals: Reverse Distribution***

Reverse distribution (also known as the "returns industry") typically refers to the return of outdated (or expired) drugs that were never dispensed by hospitals and pharmacies to pharmaceutical companies for credit. The reverse distribution industry was born in the late 1980s and early 1990s

after passage of the Prescription Drug Marketing Act in 1987 (PDMA). Prior to passage of the PDMA, returns were largely handled by pharmaceutical wholesalers and manufacturing representatives. However, there were widespread problems with diversion (that is, theft and resale) of the returned products. The PDMA prevents returns through these channels. The reverse distributors provide the service of collecting the drugs from the hospitals, usually by mail, and processing the returns for credit from the pharmaceutical companies. Traditionally, reverse distribution is only intended to be used for pharmaceutical drugs that could potentially be returned for credit. Each pharmaceutical manufacturer has policies on what is or is not returnable.

There are approximately 6,000 hospitals in the United States and tens of thousands of pharmacies. Virtually all of them contract with reverse distributors. The large reverse distributors also contract with pharmaceutical companies to ensure proper disposal of their returned product after the hospital or pharmacy has been credited. Reverse distributors therefore send some pharmaceutical waste to other reverse distributors that are contracted to handle a particular manufacturer's products.<sup>61</sup>

Reverse distributors have developed a set of "core competencies" that help them play a beneficial role in the current medical system, and that could be expanded upon to ensure greater product stewardship and less water-based disposal of pharmaceuticals. Some of the benefits of the reverse distribution model are that it:

- Centralizes outdated drugs into a finite number of warehouses which can be monitored for compliant hazardous waste disposal procedures
- Removes outdated drugs from the market in a systematic fashion, thereby reducing diversion possibilities
- Could provide the infrastructure for national consumer take-back programs in the future<sup>62</sup>

Only about 15 percent of pharmaceuticals are considered either hazardous under RCRA or other federal standards. About 70 percent of pharmaceuticals come from households and are therefore exempt from RCRA regulation under the household hazardous waste exclusion.<sup>63</sup> Therefore, concerns about complying with RCRA regulations only apply to a small portion of total pharmaceuticals.

#### ***b) Long Term Care and Other Institutional Facilities***

One barrier to participation in reverse distribution by many LTCFs is that, like households, they are non-DEA registrants. Most controlled substances used at LTCFs are flushed because they cannot be taken back by a DEA registrant. (Interestingly, the DEA has adopted an exception to this limitation to allow LTCFs in Kentucky to dispose of their controlled substances via reverse distribution). In addition, if a skilled nursing facility is classified as a "business," its pharmaceutical hazardous waste does not qualify for the household exemption under RCRA. At the same time, pharmaceutical companies typically will not give credits to patients at long-term care facilities for returned pharmaceuticals. As a result, LTCF's are largely operating separately from the reverse distribution system.

An amendment to the DEA's regulations allowing reverse distributors to receive controlled substances from LTCFs, and a funding source for reverse distributors to accept non-creditable, non-hazardous pharmaceuticals would likely increase the amount of pharmaceutical products from this source being disposed of properly rather than flushed.

Another option for handling some pharmaceuticals from these facilities in the past has been to return unused (but not outdated) products to the long term care pharmacies that serve them, for repackaging and potential reuse. The payer source (whether the state Medicaid program or a private insurer) could then be credited for the amount of the returned pharmaceutical that was reused. This has been a common practice under Medicaid in some states. However, when Medicare Part D was enacted, it did not contain a provision allowing for crediting and reuse of returned unused drugs. As a result, for those people receiving prescription coverage under Medicare Part D, the long term care pharmacies cannot reuse unused medications and those pharmacies are reusing fewer pharmaceuticals, and are disposing of more of them.

These statutory and regulatory limitations are preventing much more widespread use of reverse distribution as a means of ensuring proper disposal of pharmaceuticals and protection of water sources. Efforts to reform these regulations so that all the environmental impacts of disposal are considered would improve this situation.

### *c) Households: Take-Back Programs*

In response to the gap in responsible disposal options for households, many groups and local governments have begun creating “take back” programs as one alternative to flushing. Each program is set up differently. For example, various programs are administered and funded by local government, or pharmacies, or pharmaceutical companies, or non-governmental organizations, or other groups. The programs can involve permanent collection boxes set up in a pharmacy, or one-day events sponsored by the local law enforcement agency, or special envelopes distributed to consumers who then mail their leftover drugs to the appropriate agency.

As with LTCFs, organizers of household pharmaceutical take-back programs are hindered by the DEA’s regulations regarding controlled substances. Other considerations also apply, such as federal privacy laws requiring organizers to destroy private information on the medical containers. In addition, some organizers face problems convincing regulators, legislators, and pharmacists that the benefits of these take-back programs are justified by the costs. Sometimes, in the minds of the policymakers, the pounds of pharmaceuticals collected do not give rise to a solid waste issue; in fact, as noted earlier, preventing diversion and accidental poisonings is often a more powerful motivator than environmental concerns.

There are a very large number of take-back initiatives on-going in the United States. Appendix D provides a more expansive list of areas that have a take-back program of some sort. In addition, the Illinois-Indiana Sea Grant has compiled a great survey of model programs.<sup>64</sup> Generally, data about the effectiveness of these programs in reducing disposal into drains and toilets are still being collected and analyzed. There are a few programs worth noting.

The Washington State Unwanted Medicine Return Pilot Program allows residents to return to select pharmacy locations their unwanted medications, which are then disposed at a hazardous waste facility.<sup>65</sup> The pilot program, which has collected more than 5,000 pounds of medicines, includes a system that screens the returned drugs for contaminants and then sends them through a reverse distributor to the waste facility. The cost of the program is borne by the program itself (through funding from various grants), rather than the pharmacies.

In British Columbia, Canada, a very successful pharmaceutical take-back program funded by pharmaceutical companies has been underway since 1996, when the pharmaceutical industry voluntarily began a stewardship program.<sup>66</sup> With participation from nearly 93 percent of the pharmacies, organizers attribute the success of the program to several factors: outreach to the

pharmacy certification boards, the simplicity of the program, the low cost of the program, and the support of pharmacists who view this program as providing enhanced service to their customers.<sup>67</sup> Although the success of this program makes it a notable model, one major difference between Canadian law and U.S. law makes the model difficult to replicate in the United States. Unlike the strict U.S. laws regulating the custody of controlled substances, Canada regards any substance that has been dispensed to a customer as a household chemical, which requires no further special handling.

Finally, driven by concerns about increasing incidence of prescription drug abuse, Maine created a mail-back program in collaboration with the U.S. Postal Service and the Attorney General.<sup>68</sup> Similarly, one of the largest reverse distributors in the country is currently engaged in a pilot mail-back project in two counties in Wisconsin.<sup>69</sup>

These pilot programs have demonstrated that there are ways to deal with the problem of unwanted pharmaceuticals that do not involve flushing or throwing in the trash.

#### **D. EFFORTS TO ADDRESS UNINTENTIONAL RELEASES FROM AGRICULTURE**

There is a significant amount of activity and advocacy taking place to address the eroding efficacy of antibiotics, a public health crisis that the UCS has referred to as “the Ticking Time Bomb.” By contrast, while some work has been done, so far the development of regulatory, litigation, or legislative strategies to address the issue of hormone use by CAFOs, has not received much attention or resources.

##### **1. Education and Outreach**

According to the UCS and others, the CAFO operators are using antibiotics primarily as growth promoters and to prevent diseases and illnesses more likely to occur given the crowded and stressful conditions in which livestock and poultry are produced. These non-therapeutic uses have been the focus of an extensive campaign to reduce the use of antibiotics at factory farms. Leaders of the campaign include the UCS, the Food Animal Concerns Trust, the Institute for Agriculture and Trade Policy (IATP), and the Environmental Defense Fund (EDF). Their campaign includes extensive public education efforts including reports (such as the UCS report “Hogging It”) and fact sheets; pressure on regulatory authorities, particularly the FDA; support for legislation in Congress; and efforts to move the market via corporate campaigns and engagement with large corporations and institutional purchasers (like McDonald’s, Burger King, Panera, and Bon Appetit).

Although the bulk of concern and advocacy resources regarding pharmaceutical pollution from CAFOs have been focused on antibiotics, hormone pollution is also a cause of concern. Although to a lesser degree than antibiotics, hormones are also used in some food animal operations as growth promoters. Some organizations including the IATP, the Physicians for Social Responsibility (PSR), and the Consumers Union are doing work in this area, primarily focusing on public education or reducing public demand for hormone-free food products via consumer action.

##### **2. Litigation**

Under the CWA, it is illegal to discharge a pollutant from a “point source” into a water of the United States without a permit. CAFOs are specifically defined in the CWA as a “point source” requiring a permit for discharge of pollutants. Nevertheless, application of the CWA to CAFOs has historically been, and continues to be, extremely limited. As the number of factory farms grew rapidly in the 1990s, they gained more attention due to increased instances of fish kills and pollution incidents caused by the leaking, failure, or over-topping of waste lagoons, or runoff from sprayfields

(other problems that particularly affected nearby residents include air emissions, odors, and flies from the facilities). The growing concentration of CAFOs and associated problems led to increased pressure from state, local, and national environmental organizations for the EPA to use its authorities under the CWA to regulate the factory farms (there was also a rise in citizen suits against facilities).

During the Clinton Administration, the EPA spent several years developing a rulemaking procedure to require permits for most CAFOs. The end result, which satisfied neither industry nor the environmental community, was to require CAFOs to obtain permits, develop nutrient management plans (NMPs) that would outline a series of best practices, and limit the amount of animal waste sprayed on surrounding fields to agronomic rates. However, under the rules, the NMPs were not incorporated into an actual CWA permit and were thus not reviewable by the public or enforceable by citizens via citizen suits. The rule also failed to include technology-based standards to control discharges of pathogens. Most importantly, the rule failed to address the problem of overuse of antibiotics at CAFOs and the impacts on water quality.

Both industry and environmental groups (including NRDC) sued to overturn aspects of the rule.<sup>70</sup> While both sides won parts of their claims, the net result was a significant loss of authority to prevent pollution from CAFOs. Environmental groups successfully asserted that NMPs are reviewable and enforceable by the public, two key elements of most CWA permits. However, industry's victory was more sweeping and significant. Industry argued that the EPA lacked the authority to require all CAFOs to get permits, because permits are required under the CWA only for sources that discharge or propose to discharge pollution into U.S. waters. Because CAFOs do not regularly discharge pollution in the same way that a factory does, industry argued that only those facilities that actually discharge should be subject to permitting requirements. The federal Court of Appeals for the Second Circuit agreed with this argument. As a result, although those facilities that do discharge (or propose to) are required to have NMPs that are reviewable and enforceable, the number of facilities that will actually get the permits is likely to be very few because the EPA has indicated that it will not articulate in its revised rulemaking what types of facilities actually discharge or propose to discharge, which could result in the EPA only regulating facilities that are caught discharging red-handed. In addition, it is difficult to document discharges from factory farms, in part due to their rural location, and, given the lax enforcement climate of the last several years, the reality is that the CWA provides very little limit on discharges from CAFOs. Therefore, it appears that the more viable approach to addressing factory farm pollution from antibiotics is to address the amount of antibiotics being used on the factory farms.

### **3. Regulatory/Legislative**

As mentioned earlier, there are regulatory and legislative efforts, spearheaded by the KAW coalition (including the EDF, the IATP, and the Humane Society) to pressure the FDA's approval of antibiotics, especially those used for animals. (See section V, above.)

In addition, the UCS has recently focused on the role of subsidies. Their April 2008 report, "CAFOs Uncovered: The Untold Costs of Confined Animal Feeding Operations" argues that by cutting an array of subsidies to large factory farms, and adopting additional policies that would level the playing field for small and medium pasture-based animal food operations, the market dominance of the CAFOs could be reduced, along with attendant problems including the excessive non-therapeutic use of antibiotics.<sup>71</sup>

According to "CAFOs Uncovered," the industry has relied on cheap inputs (water, energy, and especially grain for feed) to support the high fixed costs of large-scale operations. Because the

government has promoted policies of inexpensive grain, CAFOs have an easier time competing with smaller pasture-based operations. The report describes another market phenomenon that has led to the strength of CAFOs:

Perhaps even more important has been the concentration of market power in the processing industry upon which animal farmers depend. This concentration allows meat processors to exert considerable economic control over livestock producers, often in the form of production contracts and animal ownership. The resulting “captive supply” can limit market access for independent smaller producers, since the large majority of livestock are either owned by processors or acquired under contract – and processors typically do not contract with smaller producers. Federal government watchdogs have stated that the agency responsible for ensuring that markets function properly for smaller producers is not up to the task.

The report recommends vigorous enforcement of anti-trust and anti-competitive practice laws, a shift in subsidies from large-scale to smaller operations, and greater monitoring and enforcement (and therefore internalization of cost) of environmental laws including the CWA, the CAA, and right-to-know laws. Some elements of these policies are pursued every four years as part of the Farm Bill. Others, such as use of anti-trust laws, are largely untried.

#### **4. Private Sector**

The KAW coalition has also worked on influencing industry practices through engagement with large-scale food businesses including restaurants and institutional food purchasers. In 2003, groups organized protests outside of selected McDonald’s and Burger King restaurants to highlight the antibiotics being used in poultry. Shortly thereafter, McDonald’s announced its policy to direct suppliers (primarily Tyson’s) to phase out non-therapeutic use of antibiotics in meat. Other successes in this effort include the Panera restaurant’s commitment to serve antibiotic-free poultry, and T.G.I. Friday’s policy of serving antibiotic- and hormone-free beef. Although there were some successes as a result of this effort, there was not sufficient information to verify that commitments made by restaurants and other businesses were adhered to. While McDonald’s has an ability to audit Tyson’s for its compliance, that audit is not publicly available.

Health Care Without Harm (HCWH) has been active in getting health care facilities to purchase hormone-free and antibiotic free meat and dairy as a part of their overall work to change food delivery in healthcare to a more ecologically sustainable and socially responsible system.<sup>72</sup> Over 150 hospitals have signed their Healthy Food in Healthcare Pledge, and they have a number of case studies outlined on their website of hospitals that have successfully made changes.<sup>73</sup> In addition, HCWH has developed fact sheets for healthcare institutions on the connections between the use of antibiotics in agriculture, antibiotic resistance in humans, on healthy food, and a report on hospital food in Europe.<sup>74</sup> In collaboration with San Francisco Bay Area-PSR, HCWH is working with several different hospitals to promote this work and has at least five different hospital systems who participate in regular meetings to discuss their progress. A critical component of creating change is to raise physician awareness of the connection between agricultural practices and antibiotics resistance. SF-PSR is undertaking a new project that will engage healthcare providers, particularly physicians, more in this effort.

#### **E. UNINTENTIONAL RELEASES: HUMAN**

Much less attention has been focused on the impact of human excretion. Some public utilities have begun to discuss the potential problems of pharmaceuticals in drinking water, although those efforts

are still in their infancy. The National Association of Clean Water Agencies, for example, representing nearly 300 municipal wastewater treatment plants across the country, indicate that they are exploring the development of pharmaceutical take-back programs by member agencies.<sup>75</sup> They claim to support national initiatives to tackle the problem, although, realistically, there are no such strategies. The American Water Works Association (AWWA), representing over 4,700 water utilities, released a report in 2007 on their research on the efficacy of conventional and advanced water treatment processes for removing endocrine-disrupting chemicals and pharmaceuticals from water. Their findings, which are outlined in more detail later in the report, were that “Conventional coagulation, flocculation, and sedimentation are ineffective for removing the majority of target EDCs and PPCPs [pharmaceuticals and personal care products].... [and] [f]ree chlorine can remove many target compounds, depending on the structure of the contaminant; chloramines are less effective than free chlorine; ozone and reverse osmosis are more effective than free chlorine.”<sup>76</sup> Nonetheless, the topic failed to make the agenda of their four-day annual conference in June 2008.

Similarly, the EPA is currently focusing only on research concerning detection and monitoring methods for pharmaceuticals, and the environmental fate and transport of these contaminants in the water.<sup>77</sup> The EPA also claims that it is expanding its stream studies to include data on the effects on fish. However, the question of the potential human health effects is proceeding on a much slower timeline. For example, to date, the only action that has taken place is the workshop, convened in December 2008 by the National Academy of Sciences of scientific experts, to advise the EPA on methods for screening and prioritizing pharmaceuticals to determine potential risk.<sup>78</sup> We are not aware of any environmental groups directly working on addressing unintentional discharge of pharmaceuticals from human use, as most of the focus is on animal waste.

## **F. TREATING PHARMACEUTICALS IN WASTEWATER**

The extent to which pharmaceuticals enter the environment is largely determined by the nature of the wastewater treatment plant (WWTP) where they are discharged and the type of contaminant. A study of the effects of sewage treatment on 55 pharmaceuticals, for example, found an average removal rate of approximately 60 percent at a conventional sewage treatment plant (clarification, aeration, and coagulation/flocculation/sedimentation).<sup>79</sup> WWTPs successfully remove some drugs such as ibuprofen and salicylic acid.<sup>80</sup> Other drugs, however, such as the anticonvulsant carbamazepine, the lipid regulator gemfibrozil, the analgesic diclofenac, and the drug metabolite clofibric acid have not been found to be effectively degraded in most conventional plants. (See Appendix C for a table summarizing WWTP removal rates.) Furthermore, removal rates are highly variable, depending on the specific operating parameters of individual treatment plants. Performance of a WWTP in terms of plant parameters such as biological oxygen demand, chemical oxygen demand, and nitrogen removal can be a good indicator of capacity to remove pharmaceuticals.<sup>81</sup>

Advanced sewage treatment techniques such as activated carbon, oxidation by chlorination or ozonation, and membrane filtration can increase pharmaceutical removal rates to more than 95 percent.<sup>82</sup> However, even with these techniques, the most recalcitrant drugs may not be completely removed by some of these processes.

Another concern with regard to wastewater treatment is the partitioning of hydrophobic pharmaceuticals/metabolites to sludge. Although this can effectively remove the contaminants from wastewater, the partitioning creates the potential for groundwater or surface water contamination when sludge is spread on fields as an agricultural fertilizer.<sup>83</sup> Furthermore, repeated spreading of sludge may lead to its accumulation in soil.<sup>84</sup>

The search for effective treatment is hampered by the fact that there are so many different pharmaceuticals that no one technique will effectively treat all of them. In fact, the possibility of a treatment technique effectively dealing with one type of pharmaceutical while simultaneously exacerbating the effects of another one exists. It is for this reason that many experts recommend focusing on upstream solutions such as with green chemistry to, for example, maximize the uptake of drugs so that less is excreted, or reduce the quantities of pharmaceuticals used by people and animals. Nonetheless, no matter how effective programs become in minimizing pharmaceutical waste, it will be necessary to improve treatment of any dangerous concentrations of drugs found to enter the wastewater stream. While drinking water is often treated also at a drinking water treatment plant, relying on these facilities to treat for pharmaceuticals would still leave the environment vulnerable to these contaminants.

## **1. Treatment Techniques**

As mentioned earlier, in 2007 AWWA compiled results from various studies on all the various treatment processes available and under study for their effectiveness at removing pharmaceuticals (and hormone disrupting chemicals) from drinking water.<sup>85</sup> The studies targeted a few pharmaceuticals, such as acetaminophen, ibuprofen, and estradiol, based on occurrence and to incorporate a variety of chemical properties. Generally the most effective currently available wastewater treatments for the pharmaceuticals were identified as filtration with granular activated carbon and ozonation. The AWWA findings are summarized below.

Activated Carbon: The activation process for the manufacture of activated carbon creates highly porous materials with a distribution of pore sizes and surface areas. Contaminants are absorbed by attraction to and accumulation within the activated carbon. Both powdered activated and granular activated carbon have been demonstrated to be effective at removing pharmaceuticals from water/waste, with greater than 50 percent removal for most compounds.

### Oxidation and Ozonation:

Chlorine Oxidation: Chlorine is an inexpensive disinfectant that is widely used in the water industry. It is also a strong oxidating agent that can break apart chemical compounds. Chlorine and chloramine oxidation has been demonstrated to successfully remove many compounds; however, the process is selective based on chemical structure. Half of the target compounds were highly reactive – and more than 80 percent were removed, while the remaining compounds were removed at less than a 20 percent rate. The more reactive compounds generally have aromatic rings with hydroxyl, amine, or methoxy groups. Therefore, only certain pharmaceutical compounds will be removed with high efficiency. Also, free chlorine is more effective than chloramine. However, chlorine disinfectants can react with natural organic and inorganic matter in the water to form disinfection by-products, some of which have been found to be carcinogenic or to cause adverse reproductive or developmental effects in laboratory animals.<sup>86</sup>

Ozone is a similarly strong oxidant and disinfectant and is thought to be more effective than chlorination in reducing pharmaceuticals in wastewater.<sup>87</sup> Unlike chlorine, ozone decays rapidly within minutes after addition to water and does not result in disinfection by-products. Ozonation was highly effective at removing target compounds and is among the most effective strategies. More than half of the compounds had 95 percent removal within two minutes of contact with ozone. Ozone oxidized the majority of remaining compounds by more than 50 percent after 24 minutes.

UV and UV/H<sub>2</sub>O<sub>2</sub> Oxidation: Since the early 1970's, UV light-based processes were identified as promising alternatives to conventional treatment technologies for organic pollutant removal from contaminated waters. UV light oxidizes organics by directly cleaving bonds by direct photolysis or

by reacting with water to form hydroxyl radicals that are effective at oxidizing organic compounds. UV technology used for disinfection removed only a small number of target compounds. Only compounds with conjugated bonds readily absorb UV light. The addition of H<sub>2</sub>O<sub>2</sub> for advanced oxidation with UV greatly increased the removal of some compounds. Nearly all compounds showed more than 50 percent removal and the majority were oxidized by over 80 percent. However, success is highly dependent on the dose of H<sub>2</sub>O<sub>2</sub> and UV intensity.

Oxidative treatment success has been reported for clofibrac acid, ibuprofen, and diclofenac, using either O<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>/UV, or O<sub>3</sub>/ H<sub>2</sub>O<sub>2</sub>. Ozonation has been reported to be effective in the degradation of diclofenac with complete conversion of the chlorine into chloride ions. Oxidative treatment with both H<sub>2</sub>O<sub>2</sub>/UV and O<sub>3</sub> completely detoxified a mixture of carbamazepine, clofibrac acid, diclofenac, sulfamethoxazole, ofloxacin, and propranolol within one minute of treatment.<sup>88</sup>

Ozone treatment of biologically treated water from wastewater treatment plants is reported to reduce the concentration of many pharmaceuticals (measured by the parent compound) below detection limits. It has also been reported to reduce toxicity of the antibiotic lincomycin and the veterinary antibiotic enrofloxacin. This method would be useful where ecotoxicity is a concern, such as agriculture wastewater, municipal wastewater effluents from conventional activated sludge treatments, and effluents from pharmaceutical manufacturing facilities.<sup>89</sup>

Membranes: Membrane filtration separates contaminants from water based on molecular size and/or electrostatic interactions on the membrane surface. Membrane systems can be an effective technology for reducing the concentration of a diverse set of pharmaceutical compounds during both drinking water and wastewater treatment. Nano-filtration and reverse osmosis were the most effective membranes. Reverse osmosis membranes removed over 80 percent of all target compounds.

Fe-TAML: Because many pharmaceuticals in the environment are persistent fluoroaromatic compounds, they are exceptionally stable, bioactive, and toxic. The Fe-TAML activators (iron plus tetra-amido macrocyclic ligand) are comprised of an iron atom at the center, surrounded by four nitrogen atoms, which in turn are corralled by a ring of carbon atoms. Water molecules can loosely attach to the vertical pole of the iron atom as ligands. If hydrogen peroxide is present, it can displace a water ligand and create a catalyst that triggers oxidation reactions with other compounds in the solution. These catalysts can work with hydrogen peroxide to rapidly break down 17β-estradiol and 17β-ethinylestradiol within five minutes, whereas 17β-estradiol has a natural half-life of about a week and 17β-ethinylestradiol takes about twice that time to degrade naturally. In collaborative experiments with the Institute for Green Oxidation Chemistry, the researchers reported that in the lab Fe-TAMLS together with hydrogen peroxide can rapidly degrade not only estrogenic compounds, but also bacterial spores similar to those of anthrax, sulfur compounds in motor fuels, dyes in textile mill wastewater, and organic colorants discharged from pulp and paper mills.<sup>90</sup> However, it is not yet clear what the toxicity of the oxidation products may be – simply making something “disappear” is not an appropriate goal; it must “disappear” to something benign, and that is something often beyond our technological detection ability.<sup>91</sup>

## **2. Efforts to address this problem**

There are on-going studies examining the effectiveness and feasibility of various wastewater treatment technologies. A joint collaboration between the Massachusetts Department of Environmental Protection and the University of Massachusetts – Amherst is looking at treatment technologies, as well as the toxicity of pharmaceuticals (and personal care products) and the metabolites of these chemicals.<sup>92</sup>

An Arkansas company recently received a \$750,000 grant from the National Institute of Environmental Health Sciences “to study the cost-effective removal of pharmaceutical residuals from wastewater using a new hyper ozonation technology.”<sup>93</sup> The process involves using a “hyperconcentrated dissolved ozone” unit to remove microbes and chemicals from the wastewater on a large-scale basis. The grant will focus on treating antibiotic residuals, estrogen-like compounds, industrial chemicals, and bacteria generically resistant to certain antibiotics.

For a list of abstracts identifying other methods being researched, see Appendix E.

## **G. FINAL DISPOSAL OF UNUSED PHARMACEUTICALS**

As is generally the case with chemical wastes, there is no clearly preferred final disposal solution for collected, unused pharmaceuticals. Incineration and landfilling both have well-recognized problems; however, both disposal options are superior to flushing medications down the drain, where they all subsequently enter our waterways.

### **1. Incineration**

Incineration is often regarded as a desirable treatment technology for toxic or hazardous waste because materials are permanently destroyed through this means. However, as is the case with the incineration of other chemical waste, the practice of incinerating pharmaceuticals raises concerns about the efficiency, efficacy, and environmental impacts, including the air emissions and ash residue from the incinerators, the variations in temperature and burn time at which pharmaceuticals are destroyed, halogenated dioxins from burning or halogenated pharmaceuticals or containers containing polyvinyl chloride (PVC), and transportation costs and impacts to and from disposal sites.

At the international level, there are many efforts underway to ban incineration broadly and to find alternatives to incineration. Already, Costa Rica and the Philippines have banned incineration of all waste, as has Buenos Aires. GAIA is an alliance of individuals, non-governmental organizations, academics, and others who are working to end incineration, and to promote waste prevention and disposal management practices by collaborating with others around the world. GAIA's medical waste work is implemented in conjunction with HCWH, which undertakes projects to prevent incineration and to promote alternatives.<sup>94</sup>

The search for non-incineration waste disposal alternatives for chemicals is currently underway. In February 2006, the Slovakian government and UNIDO signed an agreement on a US\$20 million Global Environment Facility-funded demonstration project for the destruction of persistent organic pollutants waste, using non-combustion technologies.<sup>95</sup> Some demonstration projects are beginning to take place (such as for Fe-TAML, gas phase chemical reduction, and alkali catalyzed reactions). However, results will not likely be seen for many years.<sup>96</sup>

Finding safer alternatives to incineration is a major priority for HCWH. Again, while there are some demonstration projects beginning, more focus and energy must be put on finding commercially viable and environmentally sustainable techniques for permanently disposing of pharmaceuticals.

### **2. Landfill**

Although wastewater treatment facilities do not currently test for the presence of pharmaceuticals and although landfills do age and leak, we surmise that landfilled pharmaceuticals do not contribute significantly to contamination of drinking water.

However, aside from the possibility of small quantities of pharmaceuticals leaking from landfills, there are other environmental issues associated with using landfills, such as groundwater

contamination from solid and/or hazardous waste landfills, security and ultimate destruction at the disposal location, scavenging from trash receptacles or at the disposal location, and the need for complete destruction for certain pharmaceuticals, like controlled substances.

## IX. Recommendations for Future Action

Throughout this report, we have recommended various actions for each point in the pipeline where changes can help address aspects of pharmaceuticals in the environment. Overall, we recommend that public health advocates prioritize upstream strategies to tackle the problem wherever possible.

The following list identifies what we consider some of the most promising strategies outlined in the body of the report.

### A. DESIGN

- Incorporate green chemistry concepts into the design of pharmaceuticals to make them more biologically available and readily metabolized.
- Design degradable drugs, so that the molecules fall apart in the appropriate environment or are susceptible to chlorination.

### B. APPROVAL

- Amend FDA regulations for approving drugs to require more substantive assessment of the environmental impacts of manufacturing, using, and disposing of the drug.
- During the approval process, require companies to include studies determining the amount of API they expect will enter the waterways, and specifically assess the health impacts of drinking water contaminated with that amount of API on vulnerable subpopulations.
- Develop a classification system for new and existing drugs based on the properties of PBT, referring to the Swedish model where much of this work has been done for APIs. Require drugs to be evaluated with this system, with the highest production volume endocrine disrupting and antimicrobials first, followed by other high production pharmaceuticals of concern. Approval decisions should consider environmental impacts of priority drugs.

### C. PRODUCTION

- Incorporate green chemistry principles to reduce the amount of water and hazardous chemicals used in and released by the production of pharmaceuticals.

### D. USE

- Continue and expand existing efforts to discourage the over-prescription of drugs.
- Continue and expand existing efforts to reduce and limit the use of human use antibiotics in food animal production.
- Encourage the transition to the reduced risk drugs via a public education campaign to inform patients and care-givers of the environmental impacts of drugs that serve the same purpose. Encourage patients to ask their physician to prescribe drugs that are both effective and as environmentally safe as possible.

## **E. DISCHARGE AND DISPOSAL**

- Promote a national ban against flushing drugs down the drain or a coordinated initiative across a critical mass of states. While moving such far-reaching legislation through the Congress would likely be a slow, even years-long process, the concept of a ban on drain disposal is itself simple to understand and would likely be very popular. Moreover, it would be a difficult proposition for opponents to fight without alienating the public.

(Note: When it comes to actual implementation, monitoring and enforcement of such a ban would likely prove difficult and unpopular.)

- Establish a national mail back program for unused household pharmaceuticals. The existing reverse distribution system could provide the basic infrastructure for such a program. Two key elements for such a program to be viable would be for the DEA to amend its regulations to allow reverse distributors to accept controlled substances from households, and the identification of a funding source to pay reverse distributors for processing mail backs from households (perhaps through national legislation requiring pharmaceutical companies to pay for a mail back program, as has been done in parts of Canada).
- Develop standards for disposal of pharmaceuticals at health care facilities that do not include flushing medications down the toilets or drains. For example, pharmaceutical distributors could be required to provide all the facilities they serve with secure lock/drop boxes as repositories for unused medications.
- Amend Medicare Part D regulations to allow long term care pharmacies to repackage and reuse some unused pharmaceuticals received from skilled nursing facilities.
- Loosen the tight DEA regulations on controlled substances so that take-back programs may be more easily implemented.
- Create producer responsibility initiatives such as disposal programs that are funded by pharmaceutical manufacturers.
- Reform the RCRA to reflect changes since 1976, such as product developments in pharmaceuticals, and to strengthen disposal requirements of many pharmaceuticals currently not sufficiently regulated.
- Improve wastewater treatment systems across the country. While a discharge ban could greatly reduce the amount of pharmaceuticals entering our waterways, treatment plants will still be confronted with the challenge of removing those chemicals entering the system from excretion. Since traditional biological treatment is not adequately effective on most pharmaceuticals, additional treatment methods will be needed.

(Note: The quest for upgrading wastewater treatment to remove pharmaceuticals must be understood in the context of the state of today's wastewater treatment infrastructure. The federal government has directly invested more than \$72 billion in the construction of publicly owned treatment works and their related facilities since the CWA passed in 1972. Nevertheless, the physical condition of many of the nation's 16,000 wastewater treatment systems is poor, due to a lack of investment in plants, equipment, and other capital improvements over the years. The last several years had seen a steady decline in

federal investment in wastewater infrastructure. A 2003 EPA analysis identified a \$271 billion gap over the next 20 years between current spending and projected needs for clean water infrastructure. Thus it will be difficult to achieve this objective.)

Are there ways that the Clean Water Act or its implementation could be improved?

## **F. RESEARCH PRIORITIES**

The most important knowledge gaps that should be addressed in any efforts to characterize the environmental and human health impact of pharmaceutical water contamination are the following:

- What volume (or magnitude measured by active units) of antibiotics is produced and used in the United States for medical, veterinary, animal production, and consumer product uses?
- What volume (or magnitude measured by active units) of pharmaceuticals (and certain classes of pharmaceuticals) is in our tap water and in our waterways?
- Can these amounts cause or contribute to adverse human health effects, considering sensitive populations and their presence as a complex mixture in drinking water?
- Is there a pharmaceutical class or category of pharmaceutical of greatest concern?
- What proportion of pharmaceutical contaminants (and certain classes of pharmaceuticals) come from excretion from humans versus disposal down the toilet?
- What is the relative contribution from animal uses, especially concentrated animal feeding operations, for antibiotic and growth hormone drugs?
- What is the magnitude of waste per unit of desired product coming from manufacturing pharmaceuticals (and certain classes of pharmaceuticals), and how much of this waste is active ingredient, hazardous chemicals, or biological hazardous waste?
- What is the best disposal method to protect the environment? Is the disposal in landfills a significant source of contamination? Are there better alternatives to incineration?
- How persistent are pharmaceuticals (and certain classes of pharmaceuticals) in the environment, and how effective is conventional wastewater treatment and drinking water treatment in destroying them?
- What methods of animal husbandry allow the production of livestock and poultry without the non-therapeutic use of antibiotics important in human medicine?

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### II. Introduction

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them. The contact is Karen Steuer, Senior Officer, Pew Environment Group, The Pew Charitable Trusts, 202-887-8818, [ksteuer@pewtrusts.org](mailto:ksteuer@pewtrusts.org) to share this report with us.

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### III. Legal Framework

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<sup>7</sup> 33 U.S.C. §§ 1251-1387(2008).

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<sup>9</sup> 40 C.F.R. § 439.2 refers to “regulated pollutant[s]” but does not specifically define them. Included in the general definitions in the section, are two lists – one is “toxic pollutants”, and the other is “conventional pollutants.” They can be found at 40 C.F.R. §§ 401.15 and 401.16.

<sup>10</sup> 40 C.F.R. 439.0

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<sup>5</sup> Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D., and Snyder, S. A. Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water. *Environmental Science & Technology*, published on-line December 17, 2008, doi: 10.1021/es801845a

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<sup>7</sup> Löffler, D., Römbke, J., Meller, M., & Ternes, T. A. (2005). Environmental fate of pharmaceuticals in water-sediment systems. *Environmental Science and Technology*, 39(14), 5209-5218; Winkler, M., Lawrence, J. R., & Neu, T. R. (2001). Selective degradation of ibuprofen and clofibrac acid in two model river biofilm systems. *Water Research*, 35(13), 3197-3205.

<sup>8</sup> Buzz Cue, personal communication with Jennifer Sass, NRDC. July 30, 2008

<sup>9</sup> The Pharmacogenetics Research Network, available at <<http://www.nigms.nih.gov/Initiatives/PGRN/Background/Mission.htm>>

## V. Drug Approval

<sup>1</sup> FDA Consumer Magazine, "The FDA's drug approval process: Ensuring drugs are safe and effective." July-August 2002.

<sup>2</sup> "Guidance on general considerations for clinical trials." 62 Fed. Reg. 66113 (December 17, 1997).

<sup>3</sup> FDA, "FDA Issues Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs to Help Prevent Creating new Resistant Bacteria" (press release), Oct. 23, 2003.

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<sup>5</sup> "Factsheet: Antibiotic Resistance and Animal Agriculture" Keep Antibiotics Working, [http://www.keepantibioticsworking.com/new/resources\\_library.cfm?refID=69872](http://www.keepantibioticsworking.com/new/resources_library.cfm?refID=69872), "Keep Antibiotics Working Coalition Applauds FDA's Issuance of Final Guidance But Criticizes Failure to Set Timetable for Action and Other Weaknesses", October 23, 2003. available at <[http://www.keepantibioticsworking.com/new/resources\\_library.cfm?RefID=36452](http://www.keepantibioticsworking.com/new/resources_library.cfm?RefID=36452)> last visited December 31, 2008.

<sup>6</sup> Environmental Defense, American Academy of Pediatrics, American Public Health Association, Union of Concerned Scientists, "Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152." April 7, 2005. FDA Docket Number 2005P-0139/CP1

<sup>7</sup> "Ban on antibiotics as growth promoters in animal feed enters into effect" European Union website, December 22, 2005, available at <<http://europa.eu/rapid/pressReleasesAction.do?reference=IP/05/1687&>> last visited December 31, 2008.

<sup>8</sup> "In depth: Fluoroquinolones: Unnecessary risks" Keep Antibiotics Working, available at <[http://www.keepantibioticsworking.com/new/indepth\\_fluoro.cfm](http://www.keepantibioticsworking.com/new/indepth_fluoro.cfm)>, last visited December 31, 2008.

<sup>9</sup> "FDA Issues Order Prohibiting Extralabel Use of Cephalosporin Antimicrobial Drugs in Food-Producing Animals" *CVM Update*, July 2, 2008, available at <[http://www.fda.gov/cvm/cvm\\_updates/fdaprohit\\_extralabeluse.htm](http://www.fda.gov/cvm/cvm_updates/fdaprohit_extralabeluse.htm)> last visited December 31, 2008.

<sup>10</sup> "FDA Revokes Order Prohibiting Extralabel Use of Cephalosporin" *CVM Update* November 25, 2008, available at <[http://www.fda.gov/cvm/CVM\\_Updates/RevokesProCepha.htm](http://www.fda.gov/cvm/CVM_Updates/RevokesProCepha.htm)> last visited December 31, 2008; "FDA revokes

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planned extralabel cephalosporin use ban”, JAVMA News, December 15, 2008, available at <<http://www.avma.org/onlnews/javma/dec08/081215v.asp>> last visited December 31, 2008.

<sup>11</sup> P.L. 110-316 (August 14, 2008).

## **VI. The Production of Pharmaceuticals**

<sup>1</sup> Henderson RK, J Kindervater and J Manley “Lessons learned through measuring green chemistry performance - The pharmaceutical experience.” 2007.

<[http://portal.acs.org/portal/fileFetch/C/CTP\\_005585/pdf/CTP\\_005585.pdf](http://portal.acs.org/portal/fileFetch/C/CTP_005585/pdf/CTP_005585.pdf)>, last visited August, 2008.

<sup>2</sup> Development Document for Final Effluent Limitations Guidelines and Standards. Section 3: Industry Description. EPA-821-R-98-005; September 1998. available at <<http://www.epa.gov/waterscience/guide/pharm/techdev/>>, last visited January 2, 2009.

<sup>3</sup> *Id.*

<sup>4</sup> Donn, J. Mendoza, M. Pritchard J. “Tons of Released Drugs Taint US Water.” Associated Press. April 20, 2009.

<sup>5</sup> Personal communication between Buzz Cue, BWC Pharma Consulting, LLC and Jennifer Sass, NRDC, July 31, 2008.

<sup>6</sup> Personal communication between Buzz Cue and Jennifer Sass, NRDC. July 30, 2008.

<sup>7</sup> For example, several pharmaceutical companies including Lilly Research Laboratories, Pfizer, and Bristol-Meyers Squibb Company have won Presidential Green Chemistry Challenge Awards from the EPA over the past ten years by using green chemistry to reduce waste. See EPA Presidential Green Chemistry Challenge homepage, available at <<http://epa.gov/gcc/pubs/pgcc/presgcc.html>>, last visited March 4, 2009.

## **VII. Overuse of Pharmaceuticals**

<sup>1</sup> Smith, Elizabeth A. and Matthew C. Mireles “Track A: Safe Drug Return: Get Rid of Unused Pharmaceuticals (GROUP) Campaign” Community Medical Foundation for Patient Safety presentation at the Improving Patient Safety through Informed Medication Prescribing and Disposal Practices; Fifth Annual Maine Benzodiazepine Study Group Conference and Fourth Annual Unused Drug Return Conference, available at

<[www.mainebenzo.org/documents/GROUPCampaign.ppt](http://www.mainebenzo.org/documents/GROUPCampaign.ppt)> last visited 15 July 2008.

<sup>2</sup> U.S. Center for Disease Control and Prevention. National Center for Health Statistics. National Health and Nutrition Examination Survey.

<sup>3</sup> Kaiser Family Foundation: Prescription drug trends. October, 2004. available at <<http://www.kff.org/rxdrugs/upload/Prescription-Drug-Trends-October-2004-UPDATE.pdf>>, last visited January 2, 2009.

<sup>4</sup> Linder JA, Bates DW, Lee GM, Finkelstein JA. Antibiotic treatment of children with sore throat. JAMA. 2005 Nov 9;294(18):2315-22.

<sup>5</sup> Linder JA, Stafford RS. Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989-1999. JAMA. 2001 Sep 12;286(10):1181-6.

<sup>6</sup> BBC. “Depression pills ‘too accessible’.” Available at <[news.bbc.co.uk/2/hi/health/3579635.stm](http://news.bbc.co.uk/2/hi/health/3579635.stm)>, printed 3/30/04, accessed 7/18/08.

<sup>7</sup> *Id.*

<sup>8</sup> Kaiser Family Foundation: Prescription drug trends. October, 2004, available at <<http://www.kff.org/rxdrugs/upload/Prescription-Drug-Trends-October-2004-UPDATE.pdf>>, last visited January 2, 2009.

<sup>9</sup> *Id.*

<sup>10</sup> *Our Daily Meds: How the Pharmaceutical Companies Transformed Themselves into Slick Marketing Machines and Hooked the Nation on Prescription Drugs* by Melody Petersen, 2008; *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* by Marcia Angell, 2005; *Before you take that Pill - Why the Drug Industry May Be Bad for Your Health* by J Douglas Bremner, 2008; *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All Into Patients* by Ray Moynihan and Alan Cassels, 2006; *Generation Rx: How Prescription Drugs Are Altering American Lives, Minds, and Bodies* by Greg Critser, 2007; *Overtreated: Why Too Much Medicine Is Making Us Sicker and Poorer* by Shannon Brownlee, 2007.

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<sup>11</sup> Medicalization refers to the process whereby normal life events (losing your hair, experiencing emotions such as sadness or anxiousness, having difficulty sleeping, etc) become medical conditions requiring evaluation and treatment – including medications.

<sup>12</sup> Drug Patent Watch website, available at

<<http://www.drugpatentwatch.com/premium/preview/detail/index.php?searchtype=alpha&category=Tradename&searchstring=DETROL%20LA>> last visited July 20, 2008.

<sup>13</sup> See e.g. Business Week, “Do Cholesterol Drugs Do Any Good?” January 17, 2008 available at

<[http://www.businessweek.com/print/magazine/content/08\\_04/b4068052092994.htm](http://www.businessweek.com/print/magazine/content/08_04/b4068052092994.htm)>; Dr. Clifford J. Rosen, chair of the Food & Drug Administration committee that evaluated Avandia, in a recent commentary in *The New England Journal of Medicine*, “The Rosiglitazone Story — Lessons from an FDA Advisory Committee Meeting” available at <<http://content.nejm.org/cgi/content/full/NEJMp078167>>, last visited December 22, 2008.

<sup>14</sup> American Academy of Pediatrics: Cholesterol in Children. *Pediatrics* Vol. 101 No. 1 January 1998, pp. 141-147 <http://pediatrics.aappublications.org/cgi/content/full/pediatrics;101/1/141>; Integrity in Science Watch. Center for Science in the Public Interest. July 21, 2008; NY Times. 8-year-olds on Statins? A new plan quickly bites back. Tara Parker-Pope. July 8, 2008.

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<sup>15</sup> [http://www.prescriptionproject.org/tools/solutions\\_factsheets/files/0004.pdf](http://www.prescriptionproject.org/tools/solutions_factsheets/files/0004.pdf)

<sup>16</sup> Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med.* 2006 May 8;166(9):1021-6.

<sup>17</sup> Before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, U. S. House of Representatives; <http://www.gao.gov/archive/1996/he96212t.pdf>

<sup>18</sup> The FDA Draft Guidance for Industry “Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices” Docket No. FDA-2008.D.0053 states that “the public health may be advanced by healthcare professionals’ receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.”

<sup>19</sup> Available at <<http://www.cdc.gov/drugresistance/healthcare/default.htm>>

<sup>20</sup> Available at <<http://www.cdc.gov/Features/GetSmart/>>

<sup>21</sup> Available at <[https://members.kaiserpermanente.org/kpweb/he/list.do?name=he-topic-browse-en&fetchMask=3&category=Root%2Fhealth\\_tree%2FDiagnosis+%26+treatment%2FDrugs+%26+supplements%2F+Antibiotics](https://members.kaiserpermanente.org/kpweb/he/list.do?name=he-topic-browse-en&fetchMask=3&category=Root%2Fhealth_tree%2FDiagnosis+%26+treatment%2FDrugs+%26+supplements%2F+Antibiotics)>

<sup>22</sup> Available at <<http://www.mayoclinic.com/health/antibiotics/FL00075>>

<sup>23</sup> Personal communication with the American Academy of Pediatrics and Sarah Janssen, NRDC; see also Shea, K. “Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics” *Pediatrics* 3 September 2004, pp. 862-868 (doi:10.1542/peds.2004-1233), abstract available at

<<http://aappolicy.aappublications.org/cgi/content/full/pediatrics;114/3/862>>, last visited Dec. 22, 2008; Clinical Practice Guideline, “Diagnosis and Management of Acute Otitis Media”

Subcommittee on Management of Acute Otitis Media, *Pediatrics* 5 May 2004, pp. 1451-1465, abstract available at <<http://aappolicy.aappublications.org/cgi/content/full/pediatrics;113/5/1451>>, last visited December 22, 2008.

<sup>24</sup> McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. *JAMA* 2002;287:3096-102.

<sup>25</sup> Majeed A. Reducing antibiotic prescriptions. *CMAJ.* 2002 Oct 15;167(8):850.

<sup>26</sup> *Id.*

<sup>27</sup> Minnesota Medical Association has been active in the issue of over-prescribing and has a working group – the chair is Sam Hall, MD

<sup>28</sup> This section based on a personal communication with Dr. Ake Wennmalm, Environmental Director of the Stockholm County Council and Mae Wu, NRDC, July 22, 2008.

<sup>29</sup> See <[www.janusinfo.se](http://www.janusinfo.se)> for the English version of the classifications.

<sup>30</sup> See e.g. Gunnarsson, B and Wennmalm, A. “Mitigation of the Pharmaceutical Outlet into the Environment – Experiences from Sweden,” *Pharmaceuticals in the Environment*, Kummerer, K (ed.), 2008.

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<sup>31</sup> A research project to assess this classification program will be completed by 2012. A first publication is pending on the motivations, intentions, and expectations underlying the development and implementation of the project. Further research on expert judgment in the environmental risk assessments of the pharmaceuticals and the consistency of the classifications made so far will be completed by December 2010. Personal communication with Marlene Ågerstrand and Mae Wu, NRDC on January 9, 2009.

<sup>32</sup> Personal communication with Dr. Ake Wennmalm, Environmental Director of the Stockholm County Council and Mae Wu, NRDC, July 22, 2008.

<sup>33</sup> *Ibid.*

<sup>34</sup> See generally, the Prescription Access Litigation Project website, available at <<http://www.prescriptionaccess.org/>> last visited January 2, 2009.

<sup>35</sup> Harris, Gardiner. *Pfizer Pays \$2.3 Billion to Settle Marketing Case*. *New York Times*, September 2, 2009. <http://www.nytimes.com/2009/09/03/business/03health.html?em>

<sup>36</sup> See generally, the Prescription Project website, available at <<http://www.prescriptionproject.org/>>, last visited January 2, 2009.

<sup>37</sup> Report from the Prescription Project, “State Legislative Activity in 2007 Relating to Conflicts of Interest, Evidence-Based Prescribing, Marketing and Data Mining” October 2007, available at <[http://www.prescriptionproject.org/tools/solutions\\_reports/files/0009.pdf](http://www.prescriptionproject.org/tools/solutions_reports/files/0009.pdf)>, last visited January 2, 2009.

<sup>38</sup> H.R. 5065: Physician Payments Sunshine Act of 2008, available at <<http://www.govtrack.us/congress/bill.xpd?bill=h110-5605>> last visited January 2, 2009.

<sup>39</sup> See generally, Long Term Care Pharmacy Alliance website, available at <<http://www.ltcpa.org/>>, last visited January 2, 2009.

<sup>40</sup> See generally the Oregon Health and Science University homepage on DERP, available at <<http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/index.cfm>>, last visited January 2, 2009.

<sup>41</sup> The Federation of State Medical Boards is a national nonprofit organization representing 70 medical boards in the US.

<sup>42</sup> See generally, the PharmedOut website available at <<http://www.pharmedout.org/>>, last visited January 2, 2009.

<sup>43</sup> Subcommittee on Oversight and Investigations. “Direct-to-Consumer Advertising: Marketing, Education, or Deception?” May 8, 2008.

<sup>44</sup> Alicia Mundy “Grassley, Dingell Lead Calls For Overhauling FDA” *Wall Street Journal*, July 30, 2008; Page A4

## VIII. Pharmaceuticals Entering the Waste Stream

<sup>1</sup> “Boxall, Alistair B.A. “The environmental side effects of medication: How are human and veterinary medicines in soils and water bodies affecting human and environmental health?” *EMBO reports* 12, 1110–1116 (2004), available at <http://www.nature.com/embor/journal/v5/n12/full/7400307.html>, last visited 14 July 2008.

<sup>2</sup> Report from the Teleosis Institute on their Green Pharmacy Program, available at <[http://www.teleosis.org/pdf/GreenPharmacy\\_FullPreliminaryReport.pdf](http://www.teleosis.org/pdf/GreenPharmacy_FullPreliminaryReport.pdf)>, last visited on 3 August 2008.

<sup>3</sup> For more information about the program, see generally the Green Pharmacy Program with the Teleosis Institute. <http://www.teleosis.org/gpp-program.php>.

<sup>4</sup> Zimmer, C. “Reducing Pharmaceutical Waste.” White Paper by the Minnesota Technical Assistance Program. August 2009.

<sup>5</sup> *Id.*

<sup>6</sup> Glassmeyer, S. T., E. K. Hinchey, et al. (2009). “Disposal practices for unwanted residential medications in the United States.” *Environment International* 35(3): 566-572.

<sup>7</sup> Bound J, Voulvoulis N. Household Disposal of Pharmaceuticals as a Pathway for Aquatic Contamination in the United Kingdom. *Environ Health Perspect*. 2005 December; 113(12): 1705–1711.

<sup>8</sup> The National Association of Clean Water Agencies. November, 2005, available at [http://www.dep.state.fl.us/waste/quick\\_topics/publications/shw/meds/NACWA-PPCPWhitePaper1105.pdf](http://www.dep.state.fl.us/waste/quick_topics/publications/shw/meds/NACWA-PPCPWhitePaper1105.pdf)

<sup>9</sup> Kuspis DA, Krenzlok EP. What happens to expired medications? A survey of community medicine disposal. *Vet Hum Toxicol* 1996; 38: 48–9.

<sup>10</sup> Seehusen, DA and Edwards J. Patient Practices and Beliefs Concerning Disposal of Medications. *J of the Am Board of Family Medicine* (2006) 19:542-547.

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- <sup>11</sup> Survey by the Washington Citizens for Resource Conservation available at <http://wastenotwashington.org/Pharmsurvey.pdf>, last visited 2 September 2009.
- <sup>12</sup> Bound, *supra*, n. 135
- <sup>13</sup>  $\beta$ -adrenergic blockers are used in the treatment of hypertension, systemic, and ophthalmic disorders
- <sup>14</sup> Email communication with Jamie Page, Health Care Without Harm, Europe and Mae Wu, NRDC.
- <sup>15</sup> Ruhoy, IS and Daughton, CG. "Types and Quantities of Leftover Drugs Entering the Environment via Disposal to Sewage - Revealed by Coroner Records," *Sci. Total Environ.*, 2007, 388(1-3):137-148. Electronically available at <<http://epa.gov/nerlesd1/bios/daughton/SOTE2007.pdf>> last visited January 2, 2009.
- <sup>16</sup> *Id.*
- <sup>17</sup> Ruhoy IS and Daughton CG. Beyond the medicine cabinet: An analysis of where and why medications accumulate. *Environ Internat* (2008). In press
- <sup>18</sup> An estimated 1,329,948 g of pharma waste is disposed into the sewage system from the national deceased population. Using a typical sewage flow rate of 545,099,299 L per day, we calculated the total contribution from all deceased persons. The daily sewage flow rate is from the Clark County system, as reported in the manuscript by Ruhoy (2007), *supra* n.15.
- <sup>19</sup> The manuscript provided data on the type and amount of drugs reported by coroner's offices from the deceased population whose deaths were documented by a Coroner. This represents about 11% of deaths across the country, according to the authors, so multiplying by a factor of 9 will provide estimates for the deceased population nationwide. Based on an estimated 1329948 g of pharma waste is disposed into the sewage system from the national deceased population, and using a typical sewage flow rate of 545099299 L per day, we extrapolated that total contribution from all deceased persons. The daily sewage flow rate is from the Clark County system, as reported in the manuscript by: Ruhoy, IS and Daughton, CG. "Types and Quantities of Leftover Drugs Entering the Environment via Disposal to Sewage - Revealed by Coroner Records," *Sci. Total Environ.*, 2007, 388(1-3):137-148. <http://epa.gov/nerlesd1/bios/daughton/SOTE2007.pdf>
- <sup>20</sup> US EPA. Unused Pharmaceuticals in the Health Care Industry: Interim Report. August 2008.
- <sup>21</sup> *Id* at 5.
- <sup>22</sup> Personal communication with Joel Kreisberg, executive director of the Teleosis Institute, and Mae Wu, NRDC, June 27, 2008.
- <sup>23</sup> Oliver, D and Chapman, A. "Final Report: Pharmaceutical Waste" Local Hazardous Waste Management in King County. April 2003. Publication Number SQG -RR-6 (11/02), electronically available at <<http://www.govlink.org/hazwaste/publications/PharmaceuticalWasteSurvey.pdf>>, last visited January 2, 2009.
- <sup>24</sup> See e.g. Practice Greenhealth, which hosts seminars on RCRA compliance; U.S. Environmental Protection Agency (2006). Region 2 multiyear healthcare initiative. The CA Compass, Vol 2. Available at <http://www.epa.gov/compliance/resources/newsletters/assistance/cacompass2-2006.pdf>.
- <sup>25</sup> See e.g. U.S. EPA, "Sloan-Kettering Fined for Failure to Properly Manage Hazardous Waste", Jan. 27, 2004; see also Smith, Charlotte. Presentation "Designing a Consumer Waste Rx Disposal Program" presented at the Minnesota Air, Water and Waste Conference, February 17, 2005. available at <http://www.pca.state.mn.us/publications/presentations/hhw-050217smith-pharmaceuticals.pdf>, last visited September 1, 2009.
- <sup>26</sup> Smith, Charlotte. Presentation "Designing a Consumer Waste Rx Disposal Program" presented at the Minnesota Air, Water and Waste Conference, February 17, 2005. available at <http://www.pca.state.mn.us/publications/presentations/hhw-050217smith-pharmaceuticals.pdf>, last visited September 1, 2009.
- <sup>27</sup> Center for Disease Control, Poisonings in the United States Fact Sheet, available at <<http://www.cdc.gov/ncipc/factsheets/poisoning.htm>> last visited 29 July 2008 (identifying that in 2004, 95% of unintentional and undetermined poisonings were caused by drugs; opioid pain medications were the most common, followed by cocaine and heroin.)
- <sup>28</sup> Malloy, Elizabeth Hinchey, Susan Boehme, and Jessica Winter "Medication Disposal: What's the Problem? Impacts on Human and Environmental Health" presentation at the Indiana Hazardous Waste Task Force, Inc., workshop. June 20, 2007. Available at <<http://www.iisgcp.org/unwantedmeds/Indiana%20workshop.ppt>>, last visited 11 July 2008.

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- <sup>29</sup> See e.g. 68 Fed. Reg. 7176, 7181 (Feb. 12, 2003); see also Arikan, O, Rice C, and Codling, E. Occurrence of antibiotics and hormones in a major agricultural watershed by Desalination, 226 (1-3), 25 June 2008, Pages 121-133
- <sup>30</sup> Marks, R. “Cesspools of Shame: How Factory Farm Lagoons and Sprayfields Threaten Environmental and Public Health.” NRDC Report. July 2001.
- <sup>31</sup> *Id.*
- <sup>32</sup> Mellon (2001), *supra* n. 50.
- <sup>33</sup> Chee-Sanford, J.C., et al. Occurrence and Diversity of Tetracycline Resistance Genes in Lagoons and Groundwater Underlying Two Swine Production Facilities. *Applied and Environmental Microbiology*, April 2001. 6(4), pp. 1494-1502.
- <sup>34</sup> Boxall, A, “The environmental side effects of medication: How are human and veterinary medicines in soils and water bodies affecting human and environmental health?” *EMBO reports* 12, 1110–1116 (2004), available at <[www.nature.com/embor/journal/v5/n12/full/7400307.html](http://www.nature.com/embor/journal/v5/n12/full/7400307.html)>, last visited 14 July 2008. (“The use of antibacterials in aquaculture in the US alone is estimated to be between 92,500 and 196,400 kg per year (Benbrook, 2002), while estimates for the total use of antibacterials in US agriculture range between 8.5 and 11.2 million kg annually (Nawaz et al, 2001; Mellon et al, 2001).”)
- <sup>35</sup> Sapkota AR, et al. Antibiotic-resistant enterococci and fecal indicators in surface water and groundwater impacted by a concentrated Swine feeding operation. *Environ Health Perspect.* 2007 Jul;115(7):1040-5.
- <sup>36</sup> Chee-Sanford, *supra* n. **Error! Bookmark not defined.**
- <sup>37</sup> Union of Concern Scientists Press Release. “European Union Bans Antibiotics for Growth Promotion.” February 14, 2006. [http://www.ucsusa.org/food\\_and\\_agriculture/solutions/wise\\_antibiotics/european-union-bans.html](http://www.ucsusa.org/food_and_agriculture/solutions/wise_antibiotics/european-union-bans.html). last visited August 31, 2009.
- <sup>38</sup> National Research Council, “Costs of Eliminating Subtherapeutic Use of Antibiotics,” Chapter 7, in *The Use of Drugs in Food Animals: Benefits and Risk*, National Academy Press, Washington, D.C., 1999, 179-187.
- <sup>39</sup> See e.g. EPA funding opportunities highlighting the potential environmental concern with steroid use in CAFOs, available at <[http://es.epa.gov/ncer/rfa/2006/2006\\_star\\_cafos.html#SUMMARY](http://es.epa.gov/ncer/rfa/2006/2006_star_cafos.html#SUMMARY)>, last visited January 2, 2009.
- <sup>40</sup> Ruhoy (2008), *id.* (citing Kostich MS, Lazorchek JM. Risks to aquatic organisms posed by human pharmaceutical use, *Sci Total Environ* 2008; 289(2-3):329-39 as an example of using this approach to estimate the types and amounts of active ingredient introduced to sewage as an unintentional result of their intended use.)
- <sup>41</sup> Bound, *supra* n. 135.
- <sup>42</sup> Malloy, *supra* n. 28.
- <sup>43</sup> In Maine alone, prior to promulgation of Medicare Part D, the state received refunds for unused drugs totally \$1.4 million annually. After Medicare Part D that practice was prohibited, that revenue was lost and all the waste entered the waste stream. Personal communication with Steven Grissett and Mae Wu, NRDC.
- <sup>44</sup> For more information, see <<http://www.PQMD.org>> and <<http://www.PSF-ci.org>>.
- <sup>45</sup> The Athens Declaration, available at <<http://www.mainebenzo.org/athensdeclaration>>, last visited January 2, 2009.
- <sup>46</sup> “Proper Disposal of Prescription Drugs” Office of National Drug Control Policy, February 2007. available at <[http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper\\_disposal.html](http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html)>, last visited 11 July 2008.
- <sup>47</sup> SmaRxT Disposal program. Press release, “Medicine Disposal Partnership will Encourage Public to Flush Less, Crush More” 17 March 2008, available at <<http://www.fws.gov/news/NewsReleases/showNews.cfm?newsId=BD972725-A176-1841-9F1266DD535BE6B1>> last visited 3 August 2008.
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- <sup>49</sup> Garamon, J. “Program Extends Drug Shelf-life. American Forces Press Service.” March 29, 2000, available at <<http://www.defenselink.mil/news/newsarticle.aspx?id=44979>>, last visited January 2, 2009.
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- <sup>51</sup> 22 MRSA §2700 Effective 7/1/05. Unused Pharmaceutical Disposal Program, available at <<http://janus.state.me.us/legis/statutes/22/title22sec2700.html>> last visited 11 July 2008.

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- <sup>53</sup> Illinois-Indiana Sea Grant Disposal of Unwanted Medicines: A Resource for Action in Your Community, Chapter 5, available at <<http://www.iisgcp.org/unwantedmeds/updatedToolkitMaterials/5.0Legislation.pdf>>, last visited December 31, 2008.
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- <sup>56</sup> Illinois Safe Pharmaceutical Disposal Act. Public Act 096-0221.
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- <sup>59</sup> PSI Pharmaceutical Project. Website available at <<http://www.productstewardship.us/displaycommon.cfm?an=1&subarticlenbr=182>>, last visited January 2, 2009
- <sup>60</sup> *Id.*
- <sup>61</sup> To give a sense of the amount of material passing through the reverse distribution system, in 2006, Capital Returns, which is one of the three largest reverse distributors, disposed of six million pounds of non-hazardous waste and 350,000 pounds of RCRA hazardous waste. These figures do not include what was sent by Capital Returns to another reverse distributor for another manufacturer.
- <sup>62</sup> These bullets are modified from Powerpoint presentations by Charlotte A. Smith, President of PharmEcology Associates, and Mary Hendrickson, Director of Quality and Regulatory Affairs for Capital Returns, Inc. They are both experts in reverse distribution.
- <sup>63</sup> 40 C.F.R. 261.4(b)(1)
- <sup>64</sup> Available at <<http://www.iisgcp.org/unwantedmeds/updatedToolkitMaterials/2.0CaseStudies.pdf>>
- <sup>65</sup> Based on personal communication with Eva Dale, Washington Citizens for Resource Conservation, and Mae Wu, NRDC, 17 July 2008.
- <sup>66</sup> The Northwest Product Stewardship Council’s website briefly outlines the Canadian programs at <http://www.productstewardship.net/productsPharmaceuticalsIntlprograms.html> (last accessed 7/24/2008).
- <sup>67</sup> Personal communication between Ginette Vanasse, Executive Director of Post-Consumer Pharmaceutical Stewardship Association, and Mae Wu, NRDC on July 3, 2008.
- <sup>68</sup> *See generally* Safe Medicine Disposal for ME Program website, at <<http://www.safemeddisposal.com/>>, last visited December 31, 2008.
- <sup>69</sup> *See generally* Waukesha County New Mail Back Pilot Medicine Collection Program, at <<http://www.waukeshacounty.gov/page.aspx?SetupMetaId=11136&id=19810>>, last visited December 31, 2008.
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