Minding the Gap: Research Priorities to Address Pharmaceuticals in the Environment

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Health Care Without Harm has initiated a research collaborative coordinated by faculty of the University of Illinois at Chicago School of Public Health, with support from the Pioneer Portfolio of the Robert Wood Johnson Foundation, aimed at stimulating collaborative research around health and safety improvements in health care. The Research Collaborative is designed to increase the evidence base concerning the impacts of design, construction, organization, operations, materials and chemicals in the health care sector on patient, worker and environmental safety.

This paper is the fifth in a series of papers in which the Collaborative provides research and analysis of factors influencing patient, worker and environmental safety and sustainability in the healthcare sector. The editors of this series are Peter Orris, MD, MPH and Susan Kaplan, JD.

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EXECUTIVE SUMMARY

Pharmaceuticals save lives and improve the quality of life. But these properties come with an environmental downside. Minute amounts of non-therapeutic levels of pharmaceuticals can be found in our waterways, generating scientific and public concern about the potential environmental and human health impacts associated with these exposures. For more than two decades, scientific studies have cataloged the biologic activity, toxic effects and hormone-disrupting impacts from pharmaceuticals to wastewater effluents and drinking water sources. Despite the growth of this body of scientific evidence from government reports, academic research, and non-profit studies, there are opportunities for additional research to mitigate and eliminate pharmaceuticals from harming the environment while simultaneously maintaining their efficacy to treat disease and ameliorate suffering.

Health Care Without Harm (HCWH), an international nonprofit coalition with more than 450 member organizations that promotes environmental responsibility for health care through a series of practice changes, looks to include pharmaceutical stewardship as part of its efforts. In order to develop and conduct research on the impact of the health care built environment, operations, and collateral impact of chemicals and pharmaceuticals on patient and worker safety and environmental sustainability, HCWH initiated a Health Care Research Collaborative. The Collaborative is coordinated by faculty of the University of Illinois at Chicago School of Public Health, with support from the Pioneer Portfolio of the Robert Wood Johnson Foundation.

The purposes of this report are to 1) provide an overview of known information about the life cycle of exposure pathways of pharmaceuticals in the environment, 2) identify the gaps in our knowledge, and 3) make a series of recommendations for further research, policy discussion, and action along the pipeline of exposure pathways. Stewardship is being considered from the life cycle of pharmaceuticals, revealing five main target areas for reducing or eliminating pharmaceutical waste in the environment: design; approval and regulation; production; use; and discharge and disposal. For each area, this paper reviews existing research, identifies gaps, and presents ideas to expand research.

Pharmaceuticals are usually classified by purpose and include: human and veterinary drugs, both prescription and over-the-counter; medical agents such as chemotherapeutic drugs; and x-ray contrast media. Many pharmaceuticals undergo structural changes when metabolized by humans and animals, and the resulting metabolites may differ both in pharmacological and toxicological properties from the original medications. Methods of administration may also impact how pharmaceuticals are metabolized.

In every phase of the life cycle, pharmaceuticals may enter in the environment. Direct pathways may include manufacturing processes; waste from human or animal excretion; improper disposal, such as flushing down a toilet; the runoff from animal feeding operations; and leaching from municipal landfills. Indirect pathways of entry to the environment are also of concern. For example, wastewater that contains pharmaceuticals may be reclaimed and used for irrigation, and this water can enter the soil and potentially contaminate groundwater. As humans deplete water resources, particularly in the arid parts of the United States and the rest of the world, reclaimed wastewater increasingly becomes an important source for irrigation.

Analytical technology now allows us to detect pharmaceuticals in the environment at very low or minute concentrations. This ability will only improve with time, providing additional data to support the effects of low-level, chronic exposures of pharmaceuticals and of their harm to aquatic, and potentially human, life.

Several classes of pharmaceuticals raise particular concern: those produced and consumed in especially large quantities, those highly potent at low concentrations, and those that persist/bioaccumulate in the environment. These pharmaceuticals present special considerations because of their usage, quantity, and persistence in the environment as well as what the drug does to the body and how the body processes the drug.

We have identified five broad knowledge gaps that should receive the highest priority in terms of research to characterize the environmental and human health impact of pharmaceutical water contamination. These reflect key parts of the pharmaceutical life cycle, from design through disposal and are framed as questions that need to be addressed:

(i) How can the design of pharmaceuticals be improved to decrease bioactivity, increase absorption, reduce excretion of waste, and lessen the carbon footprint?

(ii) What mechanisms can be used to improve the approval and regulation of existing, yet redesigned, pharmaceuticals and incentivize the development of new drugs utilizing green chemistry and decreasing the impact upon the environment?

(iii) How can the production of pharmaceuticals be improved through decreasing waste, using less harmful materials in manufacturing, and reducing the carbon footprint?

(iv) Does low level, non-therapeutic chronic exposure to pharmaceuticals in the water have an effect on the usefulness of these pharmaceuticals to treat conditions or diseases? What practices can be changed to reduce the amount of pharmaceutical waste among health care providers, pharmacists, insurers, and agriculture, thereby improving source reduction and pollution prevention?

(v) What are the ways to ensure safe disposal of unused, unwanted, or expired pharmaceuticals and to improve the removal of these compounds from wastewater, and ultimately the drinking water?

As part of this research agenda, the need to define baseline volumes and amounts will be crucial. With baseline and research studies designed to address these knowledge gaps, interventions could be developed to reduce or eliminate pharmaceutical waste.

Based on existing research, specific actions can be taken now to improve the environmental impact of the pharmaceutical life cycle. In the design and production phases, we advocate the incorporation of green chemistry concepts to make pharmaceuticals more biologically available in the body and to use fewer hazardous chemicals in production. The approval phase should incorporate a persistence/bioaccumulation/toxicity classification scheme to evaluate the environmental impacts associated with priority drugs, especially antibiotics and other drugs of concern produced at high volumes. Eliminating non-therapeutic uses of antibiotics for animals would help significantly in the fight against antibiotic-resistant bacteria. Changing prescribing and dispensing practices to encourage less waste has been piloted on a small scale and could be a key strategy for further waste reduction. Disposal programs should be initiated to address disposal and discharge issues. Further research needs to be conducted to address reductions in chemical and biological activity of final non-incineration disposal.

The need for additional research is crucial to reduce and eliminate the impact from pharmaceuticals in the environment. Yet waiting years or even decades for the results of this research is not necessary. We have identified actions that can occur now and that can be studied in order to determine their efficacy and viability. We recommend focusing on upstream approaches that prevent waste as a key strategy in research and intervention development. These efforts will help to foster better pharmaceutical stewardship, decreasing harm to the environment while ensuring the lifesaving properties of pharmaceuticals when needed.

I. INTRODUCTION

Worldwide, pharmaceuticals save millions of lives by preventing and treating diseases, and improve the quality of life for those with a chronic condition. But these lifesaving properties come with an environmental downside. Recent widespread detection of pharmaceuticals in our waterways has generated public concern over the potential environmental and human health impacts associated with exposure. 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.

Health Care Without Harm, an international nonprofit coalition with more than 450 member organizations, is the leader in effecting environmentally responsible changes in health care through waste minimization, safer products, and green building. The purposes of this report from the Health Care Research Collaborative are to provide an overview of known information about the life cycle of exposure pathways of pharmaceuticals in the environment, to identify the gaps in our knowledge, and to make a series of recommendations for further research, policy discussion, and action along the pipeline of exposure pathways.

The management of pharmaceuticals throughout their life cycle is a global issue. Most of the studies reported in this paper were conducted in countries other than the United States, such as Sweden, France, Germany, Italy, Canada, and China, although some studies are drawn from the United States, reflecting the global nature of this issue. This paper builds on the Natural Resources Defense Council's review of the literature, *Dosed Without Prescription*, and explores additional ideas put forth by other countries that have successfully grappled with this issue.

II. SCOPE OF THE PROBLEM

Pharmaceuticals are usually classified by purpose. They include: human and veterinary drugs, both prescription and over-the-counter; medical agents such as chemotherapeutic drugs; and x-ray contrast media. Many pharmaceuticals undergo structural changes when metabolized by humans and animals, and the resulting metabolites may differ both in pharmacological and toxicological properties from the original medications. Methods of administration may also impact how pharmaceuticals are metabolized.

Pharmaceuticals end up in the environment through manufacturing processes; waste from human or animal excretion; improper disposal, such as flushing down a toilet; runoff from animal feeding operations; and leaching from municipal landfills. Indirect pathways of entry to the environment are also of concern. For example, wastewater that contains pharmaceuticals may be reclaimed and used for irrigation, and this water can enter the soil and potentially contaminate groundwater. As humans deplete water resources, particularly in the arid parts of the United States and the rest of the world, reclaimed wastewater increasingly becomes an important source for irrigation.

Analytical technology now allows us to detect pharmaceuticals in the environment at very low concentrations. This ability will only improve with time, providing additional data to support the effects of low-level, chronic exposures of pharmaceuticals and of their harm to aquatic, and potentially human, life.

Researchers and policy makers, especially in Europe, have been aware of the occurrence and effects of pharmaceuticals in the environment since the early 1990s. For example, the European Union began considering environmental risk assessment for veterinary and human medicinal products by developing a guideline. The guideline provided a framework to predict environmental concentrations, assess the fate of and effects of pharmaceuticals in aquatic and/or terrestrial life, and develop a base set of ecotoxicity data.[1]

In the mid-1990s, a Danish group published a seminal article that discussed the occurrence and effects of pharmaceuticals in the environment.[2] This paper contained a review of anticipated exposure routes, a brief summary of legislation from the Food and Drug Administration and the European Union, and an outline of existing information about pharmaceuticals in the environment. The authors concluded that the lack of research made it difficult to conduct a thorough environmental risk assessment, but they raised a concern about the presence of antibiotics in water and sediments stemming from the administration of antibiotics as feed additive to fish farms as growth promoters. Since publication of the Danish paper, other studies have discovered and explored the potential effects of pharmaceuticals in the environment in a wide range of places such as Taiwan, China, India, Germany, and Sweden.

In 1999-2000, the U.S. Geological Survey (USGS), through the Toxic Substances Hydrology Program, conducted a survey of United States waterways.[3] The survey showed that a broad range of chemicals found in residential, industrial, and agricultural wastewater are commonly detected as mixtures at low concentrations downstream from areas of intense urbanization and animal production. The chemicals include human and veterinary drugs (including antibiotics), natural and synthetic hormones, detergent metabolites, plasticizers, insecticides, and fire retardants. One or more of these chemicals were found in 80 percent of the streams sampled. Half of the streams contained seven or more of these chemicals.[4] This study was the first national-scale examination of organic wastewater contaminants in streams. USGS continues to analyze these and other emerging water quality issues.

There are few data that evaluate the effects on human health of exposure to low levels of pharmaceuticals. Environmental concentrations are generally found to be several orders of magnitude below therapeutic doses. Further, assessment of possible effects is greatly complicated by the presence of environmental contaminants as mixtures, not single chemicals. Lastly, little is known about the health effects or efficacy of low level, chronic, non-therapeutic exposure to medications. This last question poses a public health conundrum. How effective will medications be when a person who has been exposed environmentally may need to use them therapeutically? Will the potency of these drugs change as a result of human exposure?

In the late 1990s, the Pharmaceutical Research and Manufacturers of America (PhRMA) established the Pharmaceuticals in the Environment Task Force, which developed working groups around the issue of pharmaceuticals in the environment.[5] Specifically, the task force looked at fate and transport, human health effects, environmental risk assessment, hormones, unused medicines, treatment, and communications.[6] Currently, it concludes that all pharmaceutical compounds tested to date in drinking water pose no "appreciable risk" to human health.[7] PhRMA continues to evaluate effects of pharmaceuticals in the environment on aquatic life and ecosystems. However, the organization recommends that drain disposal of unused drugs be avoided and continues to research the sources of unused medicine and ways to best dispose of them to reduce environmental exposure.

III PRIORITIES OF PHARMACEUTICALS

Several classes of pharmaceuticals raise particular concern: Those produced and consumed in especially large quantities, those highly potent at low concentrations, and those that persist/bioaccumulate in the environment.

Additionally, pharmaceutically active compounds (or "active pharmaceutical ingredients," APIs) are complex molecules that contain different physicochemical and biological properties.[8] Two key factors affect the metabolism of a drug: its pharmacodynamics and pharmacokinetics. Simply stated, the pharmacodynamics examines what the drug does to the body, including its therapeutic effect, side effects, mechanism of drug action, and the effects of drug concentration. Pharmacokinetics looks at what effect the body has on the drug, including absorption, distribution, metabolism, elimination, and the time it takes to process the drug.[9]

Antibiotics and Hormone Disruptors

Two classes of pharmaceuticals, antimicrobials (such as antibiotics) and medications that cause hormone disruption, have been singled out as priorities. In addition to their ability to cause health harm at low concentrations, these medications are produced in high volumes of well over 1 million pounds annually. For example, the industry trade group that monitors antibiotic use in animals reports that U.S. sales in 2006 exceeded 26 million pounds, just for animal uses.[10] Other categories of pharmaceuticals that may be of concern because they are produced in high volumes are lipid regulators, anti-inflammatories and analgesics, antiepileptics, beta-blockers, antihistamines, and antidepressants, including selective serotonin reuptake inhibitors (SSRIs).[11]

Antibiotics present a major problem for several reasons. Antimicrobials can disrupt wastewater treatment processes. They have strong potential to impact ecosystems because they are toxic to bacteria. Some also bioaccumulate; for example, studies have shown erythromycin to have a bioaccumulation factor of 45.31, which is quite high,[12] and to build up in soil.[13] More important, however, is that antimicrobials in natural waters could potentially exert selective pressure and lead to the development of antibiotic resistance in bacteria.[14]

Antibiotic resistance is caused by a number of factors, including repeated and improper use of antibiotics in humans and animals. Half the antibiotics used in livestock are in the same classes as those used in humans. As a result, the U.S. Institute of Medicine and the World Health Organization (WHO) have both stated that the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in humans.[15] The Centers for Disease Control and Prevention (CDC) has identified antibiotic resistance as one of the most pressing public health problems to face our nation.[16] Infections caused by bacteria with resistance to at least one antibiotic are estimated to kill more than 60,000 hospitalized patients each year.[17] Methicillin-resistant strains of Staphylococcus aureus, although previously limited primarily to hospital and health facilities, have become more widespread.[18] Similarly, at least 18 percent of the bacteria campylobacter (the most common cause of food-borne illness) are now resistant to the preferred antibiotic for treatment.[19] The growing threat of antibiotic resistance has been recognized by, among others, the WHO, the National Academy of Sciences, the CDC, the American Medical Association, the American Public Health Association (APHA), and the U.S. Government Accountability Office (GAO). Since 2006, the European Union has banned the use of growth-promoting antibiotics (GPAs) in farming.

Endocrine-disrupting pharmaceuticals are excreted as waste by-products from the use of birth-control pills, menopause treatments, thyroid replacements, and cancer therapies. The main synthetic hormone found in environmental samples, ethinylestradiol (EE2), is derived from human use of oral contraceptives, which are produced in great volume. EE2 is of concern because it is extremely potent at very low concentrations; a concentration of 0.1 ng/L EE2 in surface water is sufficient to induce production of the female egg protein vitellogenin in male rainbow trout.[20] In addition, this synthetic hormone has been found to bioaccumulate, reaching concentrations up to 1 million times higher in fish than in the surrounding water.[21]

In addition to human uses, hormone-disrupting steroids in livestock operations contribute to widespread environmental contamination. These pharmaceuticals interfere with not just sex hormones, but also other hormonal systems, including the thyroid gland, which is critical to proper development of the brain during fetal growth, infancy, and childhood.

Beef cattle raised in large feedlots are treated with anabolic steroids to promote the growth of muscle. One of the most common steroids used for this purpose is the androgen mimic trebolone acetate. Exposure to trebolone metabolites causes masculinization of female fish and reduced fertility at concentrations in the parts-per-trillion range.[22] Human bodies do not require larger doses of hormones to have effects; sex hormones in all vertebrate species work in the parts-per-billion to parts-per-trillion range.

Ecological Priorities

The presence of pharmaceuticals in water implicates issues beyond the obvious concerns about human health. Ecologically, pharmaceutical chemicals in waterways threaten wildlife. Exposures to animals are continuous, unlike human exposures, which are more intermittent through drinking water.

Environmental risk assessments have found pharmaceuticals, including ibuprofen, paracetamol, carbamazepine, gemfibrozil, mefanimic acid, and oxytetracycline, in some environments at levels sufficiently high to harm aquatic organisms.[23] For example, vultures in Asia have been dying from eating cattle containing relatively low concentrations of the drug diclofenac,[24] illustrating that acute effects are possible on non-target species from exposures to relatively low levels of some pharmaceuticals.

The Stockholm County Council created an environmental classification system for pharmaceuticals[25,26] when the Swedish Association of the Pharmaceutical Industry began to conduct environmental assessments of pharmaceuticals in 2005. Classification of all medications is scheduled for 2010. This system summarizes three characteristics: persistence, bioaccumulation, and toxicity. Using a ratio, it calculates risk between the predicted level that would cause harm and the predicted level that would not cause harm, creating a four-tier rating of risk from insignificant to high. This information assists healthcare providers in Sweden and the EU in comparing the environmental activity of drugs within their classifications.

The European Medicines Agency (EMEA) drafted guidelines regarding environmental impact assessment for human and veterinary medicines.[27] It proposes a tiered approach to risk assessment that begins with the derivation of an aquatic Predicted Environmental Concentration (PEC) for the drug (but not its metabolites or environmental transformation products) and an assessment of the potential for exposure. If the PEC indicates a potential for risk, additional toxicological and environmental fate data must be evaluated.

Two French researchers posed and conducted preliminary testing on a priority list of some of the most commonly detected pharmaceuticals of greatest concern for environmental impact, assessing environmental risk using EMEA guidelines as well as the PEC calculation. The researchers found that this calculation was insufficient to assess risk due to a lack of ecotoxicity data. Their recommendations included combining PECs with pharmacological and ecotoxicological data available from the literature to help define a more accurate priority list.[28]

As another example of this type of impact, the U.S. Geological Survey reported a high incidence of intersex fish in the Potomac watershed at sites of intense farming and high human population density.[29] The USGS found eggs in the testes of 75 percent of male smallmouth bass in the most densely populated and heavily farmed Potomac basin. Other research has found environmental androgens associated with masculinization in female fish living downstream of pulp mills and concentrated animal-feeding operations.[30]

As analytical technology has allowed for the detection of very low concentrations of pharmaceuticals in aquatic systems, it has become clear that these contaminants are ubiquitous. However, the risks these contaminants pose to human and ecosystem health remain unclear, although evidence is building to suggest some harm may be occurring to aquatic and animal life. Much more research is needed on the effects of exposure to these compounds.

IV. THE PIPELINE OF OPPORTUNITIES

This paper considers the entire life cycle of pharmaceuticals, revealing five main target areas for reducing or eliminating pharmaceutical waste in the environment: design; approval and regulation; production; use; and discharge and disposal. The definitions of each of these areas are described below.

Design: The design and development of pharmaceuticals to increase bioactivity and absorption, and to include tailored approaches for drug administration based upon individual patient traits like weight or genetics.

Approval and Regulation: In obtaining U.S. Food and Drug Administration (FDA) approval to market a drug, it must meet the criteria of "safe and effective."[31] Currently, no environmental impact is required to meet this criteria.

Production: Manufacturers generate thousands of pounds of waste for each pound of pharmaceutical product produced. This waste is generated throughout the world as part of the globalization of pharmaceutical production.

Use: The practice of prescribing and dispensing pharmaceuticals.

Discharge and Disposal: The discharge and disposal of pharmaceuticals is an end-of-the-pipe problem.

Drug Design

As with other environmental issues, the problem of pharmaceuticals in drinking water can be confronted at the beginning: at the top of the pipeline, where drugs are designed. One way to address the design of pharmaceuticals is through "green chemistry," or the invention, design, and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances.[32] Its principles can be applied to pharmaceutical design and production. Green chemistry would address two key challenges: better absorption of pharmaceuticals within the body and better formulation to facilitate rapid removal upon release to the environment, decreasing their persistence.

Those who have endeavored to apply green chemistry to pharmaceutical development have run into a number of problems that are found in developing any drug. On average, it takes more than a decade to develop, test, and receive approval for any new medicine in the United States, costing the manufacturer millions or billions of dollars. While some have proposed "green" alternatives to existing pharmaceuticals, to market them the manufacturer would need to revisit the drug approval process with government agencies. It is unclear how that new process would be administered. Currently, green chemistry for pharmaceuticals is being considered at a theoretical rather than an implementation level, although pharmaceutical companies are contemplating how green chemistry may help them to prevent waste and use safer chemicals and products to produce previously approved drugs.[33]

The degree to which the body metabolizes pharmaceuticals differs by medication and can vary widely. For example, 80 percent to 90 percent of the antibiotic amoxicillin is excreted in the parent form, but only 3 percent of the antiepileptic drug carbamazepine is excreted unchanged.[34] Even when pharmaceuticals are metabolized to inactive conjugates in the digestive tract, they can nonetheless remain a threat to the environment, since these conjugates frequently cleave to wastewater treatment systems and sewers, causing the original active parent compound to be released. These factors are highly relevant to the environmental impacts of these drugs. Rigorous evaluation of these impacts during the drug design phase could help minimize environmental problems without undercutting the efficacy of drugs.

Similarly, there is wide variability in the environmental persistence of drug compounds. For this reason, it appears that the occurrence of pharmaceuticals in drinking water is not related to the prescription volume of the drug.[35,36,37,38] A survey of 19 water treatment facilities did not detect the presence of that area's most frequently prescribed drug, Lipitor, in the finished water samples, while drugs that were not within the top 200 prescribed in the area were among the most frequently detected.

The pharmaceutical industry has begun to consider the incorporation of green chemistry principles into its drug development processes. Increased efforts could be expended to reduce the amount of pharmaceutical waste excreted from human bodies. Enhancing bioavailability, or designing improved delivery of drugs to target the tissues where they are needed, would decrease the required total dose for the patient.[39]

Attention might be given to designing medications in a way that would reduce substantially the inherent hazard of pharmaceuticals to the environment. For example, companies could develop drugs that "self-destruct" in the environment or create nonpolluting technologies to decompose active pharmaceutical ingredients (APIs) and their active byproducts prior to discharge to the environment.[40] Designer drugs that are "natural products" such as nucleotides or proteins would be more susceptible to degradation or denaturing in environmental media.[41] The challenge with these designs, of course, is to ensure that drugs retain their pharmaceutical activity during production, delivery to the patient, and consumption or application.

Drug Approvals and Regulatory Framework

In the United States, the Federal Food, Drug and Cosmetic Act of 1980 empowers the Food and Drug Administration to regulate pharmaceuticals. Under this Act, 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 Policy Act (NEPA).[42]

NEPA requires federal agencies to conduct environmental impact assessments of any federal action that may significantly impact the human environment and to consider the environmental effects of their actions.[43] Under NEPA, the approval of a drug is considered a "federal action" that triggers the requirement to conduct an EA. (The U.S. Environmental Protection Agency (EPA) does not have the authority to review pharmaceuticals because drugs are exempted from the Toxic Substances Control Act.) 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 1 parts per billion (ppb) in the aquatic environment or 100 ppb in soil.[44] This exemption likely includes many drugs.

Animal drugs can only be marketed if approved by FDA. All animal drugs now on the market are considered "new animal drugs," even if they have been on the market for years. Section 512 of the U.S. Code requires that a New Animal Drug Application (NADA) be denied if the Secretary of the Department of Health and Human Services finds that available data show a drug is "unsafe" for use under the proposed-use conditions or that data "do not show that such drug is safe" under its use conditions. Thus, the standards for granting and withdrawing NADA approvals are substantively identical.[45]

The manufacture, collection, discharge, and disposal of pharmaceuticals are regulated by a number of federal laws and by three different federal agencies – the Food and Drug Administration, the Environmental Protection Agency, and the Drug Enforcement Administration (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 EPA.

Food and Drug Administration

Drugs that are not generally recognized as safe and effective must be tested for safety and efficacy before FDA will allow them to be marketed. Outside of the NEPA assessment requirements, FDA does not explicitly require the consideration of environmental impacts before it approves pharmaceuticals. Moreover, because NEPA does not require FDA to take the most environmentally beneficial action, the agency is unlikely to restrict pharmaceuticals adequately from the environment. Furthermore, as noted previously, drugs predicted to occur at less than 1 ppb in the aquatic environment or 100 ppb in soil are exempted from this EA requirement.[46]

FDA provides some guidance, however, on antibiotics, which dominate 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."[47] Until recently, FDA routinely granted approval for use of antibiotics in animal feed for non-therapeutic applications, including antibiotics used extensively to treat human illnesses. In July 2005, FDA banned the use of the Cipro-like antibiotics fluoroquinolones in poultry.[48] In July 2008, FDA banned the use of third- and fourth-generation antimicrobial cephalosporins for extra-label veterinary uses. However, in December 2008 FDA reversed itself and dropped the ban in the face of overwhelming industry opposition.[49]

Antibiotics fed to livestock could provide an ideal opportunity for FDA and EPA to work jointly in developing stringent guidelines to mitigate their use while protecting public health and the efficacy of this class of drugs. This could serve as a model for further developing regulatory requirements that incorporate environmental exposure considerations.

Environmental Protection Agency

The EPA has authority to regulate the pharmaceutical industry's discharges to water and from sewage treatment plants under the Clean Water Act.[50] It also regulates the industry's industrial emissions to air under the Clean Air Act.[51] Finally, EPA regulates the disposal of pharmaceutical manufacturing waste under the Resource Conservation and Recovery Act.[52] The Safe Drinking Water Act gives EPA the authority to set health-based standards for certain contaminants that are present in drinking water.[53]

Drug Enforcement Administration (DEA)

Intentional disposal of controlled substances, or pharmaceuticals that are problematic because of their attractiveness to drug abusers and recreational users, is regulated by the DEA under the Drug Abuse Prevention and Control Act.[54] DEA regulations exclude individual consumer disposal, however, as long as the disposal is by the prescription holder. Furthermore, the DEA prohibits consumers from returning controlled substances to the pharmacies where they acquired them, or from transferring them to legitimate registrants such as reverse distributors, except in the case of a recall or a dispensing error. This prohibition creates a significant barrier for consumers, hospitals, and other entities to dispose of unwanted and expired pharmaceuticals by any method other than flushing them down the toilet or putting them in the trash.

States and municipal governments have legal and regulatory authority over pharmacy distribution, sales, and disposal, as well as drinking-water quality and protection. However, these laws vary from state to state.

While using risk assessment to set threshold limits, the European governments often invoke the "precautionary principle," which suggests that in the face of uncertainty about the toxic effects of a given chemical, a limit should be set that is thought to be safe until more information is attained. For example, the European threshold of 0.01 µg/L as a predicted environmental concentration (PEC) is 100 times more stringent than the level the U.S. FDA requires to begin an investigation. In the European Union, chemicals that cross this threshold require a more detailed assessment of their impact.[55, 56] This difference between the European and U.S. methods of gauging environmental impact influences respective policies.

Pharmaceutical Production

The quantity, and variety, of waste created during the manufacture of pharmaceuticals dwarfs the amount of finished product. The waste generated per kilogram of active ingredient produced can range from 200 kilograms to 30,000 kilograms. Among manufacturing wastes are biological compounds such as fermentation wastes, the leftover solvents when active ingredients are extracted from natural sources, and pharmacologically active reagents such as anticoagulants and chemotherapeutic agents. Manufacturing wastes also include chemicals such as cleaning agents and disinfectants used to sterilize equipment and extraction solvents that isolate and purify active ingredients.[57]

The production of pharmaceuticals is a global enterprise. Since 2003, a number of studies have demonstrated that the effluent from pharmaceutical manufacturing contains much higher levels of drugs and chemicals than the production process. In 2009, several studies evaluated the effluent produced by pharmaceutical manufacturing plants. In Patancheru, near Hyderabad, India, where approximately 90 manufacturers send wastewater to a common water treatment plant, one study detected extraordinarily high levels of a wide range of pharmaceuticals in the treated effluent.[58] This study found changes in gene expression in fish as a result of these exposures.

Further studies are examining similar concerns around the world. Another study assessed the effluent from hospitals in Norway, demonstrating that point source discharges from hospitals vary from substance to substance, resulting in a relatively small overall load.[59]

The National Health Service of England looked at procurement of pharmaceuticals and the resulting carbon emissions.[60] Procurement was defined as the manufacture and transportation of NHS-purchased goods and services. Overall, procurement constituted 60% of NHS England carbon emissions, with pharmaceuticals and medical equipment making up half of these emissions, and pharmaceuticals accounting for a fifth of total emissions. This is comparable to emissions from either the building energy use or travel sectors. Other studies are looking to replicate these findings.

The implications are quite staggering. By working with industry at a regional level as well as globally, it might be possible to lower emissions during the manufacturing process and through distribution. Specific suggestions from the NHS study to reduce carbon emissions included reducing the wasting of pharmaceuticals as a resource, which would decrease procurement costs, reducing the amount and number of pharmaceuticals prescribed without compromising medical quality; reviewing the carbon intensity with which pharmaceuticals are produced; and reviewing the manufacturing of pharmaceuticals for energy efficiency and reduction in carbon use.

Green chemistry concepts offer great potential to help address issues related to the production of drugs. Pharmaceutical companies are interested in using green chemistry as a cost reduction strategy, especially for drugs produced in high volume that do not require further regulatory review. Designing pharmaceuticals with the same therapeutic effect that use less API makes it possible to decrease the amount of drug that must be manufactured, therefore significantly decreasing production waste and the amount of drug in each dose.[61] Green chemists are also gaining some ground in reducing the use of water and hazardous solvents in the production process.

Pharmaceutical Use

Pharmaceutical consumption has increased significantly over the past two decades, leading to increased loading of pharmaceutical discharge and waste into the environment. Every month, in the US, 135 million people use prescription medicines, for a total of 4 billion prescriptions filled each year.[62] Between 1988 and 2002, the percentage of Americans who reported using prescriptions in the past month increased, as did the percentage of Americans that used three or more prescriptions. Older persons represented the biggest percentages.[63]

Prescription drug use will increase because of an aging population living longer, with more chronic diseases; a younger population with more chronic diseases, including neurobehavioral developmental disorders and obesity; and a trend toward personalized and tailored medicine.[64]

As prescription drug use increases in the United States and throughout the world, action by regulators, the medical community, and the pharmaceutical industry is needed to provide better public health and environmental protection. Greater drug use requires improved disposal mechanisms for unused drugs, increased regulatory vigilance to enhance environmental protection, and ways to address increased excretion through human waste and practices that may lead to overuse of prescriptions.

Discharge and Disposal

The pathway for pharmaceuticals entering the waste stream is characterized as either unintentional or intentional. "Unintentional releases" refers to the excretion of metabolized and unmetabolized pharmaceuticals from animals or humans. "Intentional releases" refers to the disposal of unused or expired pharmaceuticals by flushing them down the toilet, rinsing them down the sink, or throwing them into the trash. Intentional releases also include disposing of pharmaceuticals purposely as part of manufacturing products.

Within these categories, there are major differences in environmental impact. For example, pharmaceuticals unintentionally released by humans are usually excreted into a sewer system that treats the contaminants, while pharmaceuticals unintentionally released in aquaculture and agriculture are often discharged directly into the water or soil without treatment.[65]

Reliable and adequately detailed data on the volume of sales, human consumption, and disposal of pharmaceutical products are not publicly available. Therefore, only rough estimates can be made about the extent of intentional releases into the waste stream. A very high percentage of drugs – as much as 50 percent of many prescriptions and 80 percent of antibiotics – are believed to go unused, although PhRMA reports that number as only about 3 percent.[66,67] Most unused medications are either put in the trash, flushed down the toilet, or rinsed down the sink.[68] Furthermore, hospitals, long-term care facilities, and other institutions deal with large quantities of unused pharmaceuticals, and their contribution to the pharmaceutical waste stream is estimated to be between 20 percent and 65 percent.[69]

In addition, disposal of deceased people's unused medications may increase the concentration of pharmaceuticals in water entering sewage treatment systems from drains (toilets and sinks) by 2.4 parts per million.[70,71] A variety of options exist to tackle this problem, such as community take-back programs, mail-in programs, and reverse distribution.

Modeling may be used to estimate the unintentional release of human excretion. These models predict the amount of API that enters the environment by analyzing information about usage, rates of excretion of API, and effectiveness of treatment techniques used by wastewater and drinking water facilities.[72] However, to date no studies have tested the accuracy of such models.

The unintentional release of pharmaceuticals, particularly antibiotics and steroids, from the agricultural sector significantly impacts the environment. An estimated 2 trillion pounds of animal wastes are produced annually in the United States; between 25 percent and 75 percent of antibiotics are excreted unchanged in feces and can persist in the soil after land application.[73,74] Concentrated animal-feed operations contribute highly to the problem of antibiotic resistance, particularly because of the large-scale use of antibiotics for non-therapeutic uses.[75] The EU has already banned agricultural use of non-therapeutic antimicrobials that are important in human medicine. In the United States, the National Research Council estimates that a total ban on antibiotic use would increase the price of meat only between $0.013 to $0.06 per pound.[76]

Treating Pharmaceuticals in Wastewater

Two factors largely determine which pharmaceuticals enter the environment: the nature of the wastewater treatment plant (WWTP) where they are discharged and the type of contaminant. WWTPs can successfully remove some drugs, but most conventional plants do not effectively degrade other pharmaceuticals.[77,78,79] Removal rates are highly variable. Plant parameters such as biological oxygen demand, chemical oxygen demand, and nitrogen removal can be good indicators of capacity to remove pharmaceuticals.[80] Advanced sewage treatment techniques such as activated carbon, oxidation by chlorination or ozonation, and membrane filtration can increase pharmaceutical removal rates. However, even with advanced techniques, the most recalcitrant drugs may not be completely removed from wastewater.

Another concern with wastewater treatment is the partitioning of hydrophobic pharmaceuticals/metabolites to sludge. Although partitioning can effectively remove contaminants from wastewater, this process creates the potential for groundwater or surface water contamination when the resulting sludge is spread on fields as an agricultural fertilizer.[81] Furthermore, repeated spreading of sludge may lead to the accumulation of pharmaceuticals in soil.[82]

The search for effective wastewater treatment is complicated by the diversity of pharmaceuticals. No single technique will effectively treat all of them. The possibility exists for a treatment technique that effectively deals with one pharmaceutical while simultaneously exacerbating the effects of another one. For this reason, many experts recommend focusing on upstream solutions such as green chemistry, which maximizes the uptake of drugs so fewer are excreted, or reduces the quantities of pharmaceuticals people and animals use. Regardless of the effectiveness of these programs in minimizing pharmaceutical waste, it will still be necessary to improve treatment of dangerous concentrations of drugs that enter the wastewater stream.

Collection of Unused Pharmaceuticals

Collection programs for unused, unwanted, or expired pharmaceuticals are not new. A number of countries have some form of pharmaceutical collection program. In 1998, Australia established a system through community pharmacies for the collection and destruction (through high-temperature incinerator) of unwanted and out-of-date medicines, known as the Return Unwanted Medicines (RUM) Project.[83] Most of the provinces of Canada have a collection system, generally through community pharmacies, and use incineration as the final end-point.[84] Spain and Portugal have collection programs as well. Governments fund the programs in these countries. In France, the pharmaceutical industry funds the nationwide collection program. In all cases, a massive education program accompanied the collection program.

U.S. collection programs have been hit-or-miss, very locally based, and rely on grant funding. The lack of consistency and access are barriers to developing a nationwide strategy, as is the issue of determining who should pay for collection and disposal. Additionally, before further development can occur, significant legal and regulatory issues need to be addressed at the federal level.

Final Disposal of Unused Pharmaceuticals

Like many chemical wastes, unused pharmaceuticals have no clearly preferred final disposal solution. Incineration and landfilling have well-recognized problems; however, both disposal options are less problematic than flushing medications down the drain.

Incineration is often regarded as a desirable treatment technology for toxic or hazardous waste because the materials are permanently destroyed. However, this practice raises concerns about efficiency, efficacy, and environmental impacts, including air emissions and ash residue from the incinerators, the variations in temperature and burn time that destroy pharmaceuticals, halogenated dioxins from burning or halogenated pharmaceuticals or containers containing polyvinyl chloride, and transportation costs and impacts to and from disposal sites. The biggest obstacle is finding commercially viable and environmentally sustainable techniques for permanently disposing of pharmaceuticals.

Other techniques such as activated carbon, oxidation, activated sludge, nanofiltration and reverse osmosis membranes have been tried to remove pharmaceuticals from water.[85] The published literature indicates that current technologies do not address the following: 1) the impossibility of eliminating all pharmaceuticals from drinking water, especially those that are considered endocrine-disrupting chemicals; 2) mixing with other chemicals in the water to cause additional harmful agents that would then need further treatment; 3) necessitating a dose well beyond a disinfecting level; or 4) requiring significant energy to remove both pharmaceutical compounds and their disinfectant byproducts. While some of these technologies are more promising than others, none of these eliminate pharmaceuticals from the water or consistently render them both biologically and chemically inert. This presents an opportunity to address this problem through technology development.

Wastewater treatment facilities do not test for the presence of pharmaceuticals as part of regulating impurities, and landfills age and leak. Nevertheless, the research suggests that pharmaceuticals in landfills do not contribute significantly to contamination of drinking water. Aside from the possibility of pharmaceuticals leaking from landfills, there are more significant environmental issues associated with pharmaceuticals stored in 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 drugs, like controlled substances.

V. RESEARCH RECOMMENDATIONS

Throughout the discussion of the life cycle of pharmaceuticals, there are many opportunities to pose research questions. Some of these questions may be answered through rigorous experimental designs, others through public health evaluations, and others through models (Table 1). The purpose of posing these questions is to "mind the gap" in research and to suggest ideas for further study.

Table 1. Potential Research Areas in the Life Cycle of Pharmaceuticals

Life cycle	Questions
Design	How persistent are pharmaceuticals in the environment? Are there differences in classes of pharmaceuticals?
	How can green chemistry be used to improve bioactivity, absorption of pharmaceuticals and reduction of excretion waste?
	What is the environmental impact of designing drugs using a green chemistry approach?
	What is the economic impact of designing drugs using a green chemistry approach?
	How can measurements be standardized to assess the design of pharmaceuticals across countries, since pharmaceutical companies are global as are their effects upon water?
	What is the carbon footprint for the design of pharmaceuticals?
Approval and Regulation	When a pharmaceutical is redesigned using green chemistry to increase its bioactivity and decrease excretion waste, will the pharmaceutical have to go through the full FDA approval process as a "new" drug?
Production	What is the magnitude of waste per unit of desired product from manufacturing pharmaceuticals?
	How much of the production waste is active ingredient, hazardous chemicals or biological hazardous waste?
	How can green chemistry be used to improve the production process and reduce excretion waste?
	What is the carbon footprint for the production of pharmaceuticals?

Life cycle	Questions
Use	Does low level, non-therapeutic chronic exposure to pharmaceuticals in the water have an effect on the usefulness of these pharmaceuticals to treat conditions or diseases?
	How can prescribing practices change? How can dispensing practices change? What are the ways to change payments to encourage changes in prescribing and dispensing of pharmaceuticals?
	Would a voucher program to replace pharmaceutical samples for new medications work on a large scale?
	What kind of educational programs would be helpful to train health providers, pharmacists, insurers, and groups that contract with insurance companies about this issue?
	Would having information about a pharmaceutical's environmental impact have an effect upon prescribing or dispensing practices?
	Would reducing or eliminating high-volume non-prescription medications sold at big-box stores reduce the amount of pharmaceutical waste?
	What is the carbon footprint for using pharmaceuticals?
Discharge and Disposal	What is the volume (or magnitude measured by active units) of pharmaceuticals (and certain classes of pharmaceuticals) in our tap water and in our waterways?
	What proportion of pharmaceutical waste comes from humans as opposed to pharmaceuticals from animal uses?
	How much waste comes from people's homes or institutions?
	Does low level, non-therapeutic chronic exposure to pharmaceuticals in the water have an adverse human health effect? Is there a synergistic effect with a complex mixture in the drinking water?
	How can pharmaceuticals be removed from wastewater and what is the most effective way to remove these compounds? How can complex mixtures of pharmaceuticals be removed from the drinking water?
	What do other countries do about disposing of controlled substances? DEA controls this classification of medications, and until this is addressed, collection programs will be very limited.
	Would including a green label on prescriptions have an effect on safer disposal options?
	What is the carbon footprint for the disposal of pharmaceuticals?

VI. POLICY RECOMMENDATIONS

Although the purpose of this paper is to address research gaps, policy issues are raised as well. The following is a summary of policy recommendations as described through the life cycle:

Design: The safety of new pharmaceuticals could be greatly improved with consideration of the environmental impacts inherent in drugs at the outset of their design and development. A key aspect of reducing pharmaceutical waste will be to design medications through green chemistry. Additionally, green chemistry could be used in the design to increase the absorption of pharmaceuticals in the subject taking that medication, thereby reducing the waste generated through excretion.

Approval and Regulation: In the United States, the approval process is long and laborious, but the rigor has slipped over the last decade. For example, drugs such as Vioxx have been approved for use with noted side effects, including death, that have caused their removal from the market. A revamping of the federal policies that govern the approval and regulation of pharmaceuticals is not only necessary but will be essential with the development of new delivery systems and individualized medicine. State policies that restrict disposal of medications complicate the regulation and should be monitored to assess how this impacts upon federal policies. Furthermore, which federal agency has regulatory control of the development, distribution, access, and disposal of pharmaceuticals is complex and requires interagency coordination that currently does not exist.

Production: Up to thousands of pounds of waste are created for each pound of pharmaceutical product produced. Before production begins, undertaking a pollution prevention assessment of upstream opportunities to reduce waste could clarify how much of this waste is necessary. Green chemistry can be applied not only to pharmaceutical design, but will increase the efficiency of the manufacturing process while reducing the amount and toxicity of chemicals needed in this process.

Use: To decrease pharmaceutical waste, the need to move the issue more upstream is essential. The focus should shift from disposal, to prescription and prescribing practices. Educating key stakeholders like health professionals and pharmacists will influence how pharmaceuticals are prescribed and ultimately dispensed. Changes in formularies to include vouchers for new prescriptions may be a key component in changing costs while providing a "sample" of new medications for patients to try. Regarding pharmaceutical use with livestock, eliminating the non-therapeutic use of antibiotics by altering farming practices is essential for insuring the future efficacy of this class of drugs. Lastly, having access to information about which pharmaceuticals have similar bioactivity but are less harmful to the environment should be made available to health care providers and pharmacists.

Discharge and Disposal: Currently, there are few solutions that address discharge and disposal. None of them offer a "best" practice. New research needs to be done to improve disposal practices and decrease discharges. For example: If pharmaceuticals are designed and manufactured with green chemistry, then there should be a smaller amount for disposal; if prescribing and dispensing practices change, again, quantities for disposal should be lessened; if livestock are not treated with non-therapeutic antibiotics, there will be smaller quantities generated from that sector. But these are currently just "ifs." Additional research and investment capital is needed to explore the most effective way to reduce chemical and biological activity of pharmaceuticals through non-incineration means. Concurrently, the pharmaceutical industry needs to be held accountable and be required to develop programs that mail-in or take-back their products for disposal beyond the pharmacy. In many countries besides the United States, successful government-industry partnerships exist that already encourage this practice and that could easily be replicated, but it requires the political will to make this idea into a reality.

VII. CONCLUSION

Despite their ability to improve our quality of life or extend our lives, diverse classes of pharmaceuticals are getting into our waterways and ultimately into our tap water at levels that are detectable and in forms that are biologically active. The most concentrated sources of pharmaceuticals include those discharged or released from livestock farms; those that are excreted with human waste; and that generated through the life cycle of pharmaceuticals, from design and production, to use and excretion, to disposal, generating significant excess that ends up as waste.

Substantial data gaps leave fundamental questions unanswered at this time. No epidemiological studies have been done to link health outcomes with pharmaceutical contamination in water. Because of compounding limitations in experimental design, no data have been reported on the toxicity of these compounds during incidental, lower-dose exposure to non-target populations.

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

(i) How can the design of pharmaceuticals be improved to decrease bioactivity, increase absorption, reduce excretion of waste, and lessen the carbon footprint?

(ii) What mechanisms can be used to improve the approval and regulation of existing, yet redesigned pharmaceuticals and incentivize the development of new drugs utilizing green chemistry and decreasing the impact upon the environment?

(iii) How can the production of pharmaceuticals be improved through decreasing waste, using less harmful materials in manufacturing, and reducing the carbon footprint?

(iv) Does low level, non-therapeutic chronic exposure to pharmaceuticals in the water have an effect on the usefulness of these pharmaceuticals to treat conditions or diseases? What practices can be changed to reduce the amount of pharmaceutical waste among health care providers, pharmacists, insurers, and agriculture, thereby improving source reduction and pollution prevention?

(v) What are the ways to ensure safe disposal of unused, unwanted, or expired pharmaceuticals and to improve the removal of these compounds from wastewater, and ultimately the drinking water?

As part of this research agenda, the need to define baseline volumes and amounts will be crucial. With baseline and research studies designed to address these knowledge gaps, interventions could be developed to reduce or eliminate pharmaceutical waste.

We recommend taking various actions at each point in the pipeline where changes can help address aspects of pharmaceuticals in the environment. In the design and production phases, we recommend incorporation of green chemistry concepts to make pharmaceuticals more biologically available in the body and to use fewer hazardous chemicals in the production. The approval phase should incorporate a persistence/bioaccumulation/toxicity classification scheme to evaluate the environmental impacts associated with priority drugs, especially antibiotics and other drugs of concern produced at high volumes. Eliminating non-therapeutic uses of antibiotics for animals could help significantly in the fight against antibiotic-resistant bacteria. Changing prescribing and dispensing practices to encourage less waste has been piloted on a small scale and could be a key strategy for reducing waste. Disposal programs should be initiated to address disposal and discharge issues. Further research needs to be conducted to address reductions in chemical and biological activity of final non-incineration disposal. Upstream strategies should be incorporated at every stage of the development process to prevent potential contamination and exposure while reducing and minimizing waste wherever possible.

Pharmaceuticals are crucial to maintaining health and improving the quality of life. By identifying gaps in current research, Health Care Without Harm and the Health Care Research Collaborative point out opportunities to make substantive changes at every stage of the pipeline to reduce the harmful affects associated with pharmaceutical production and use. Acting on these recommendations to improve the design, approval, production, use, and discharge or disposal of pharmaceuticals is essential to efforts to reduce the harm associated with pharmaceutical health care. These recommendations also provide a groundwork for agencies of the federal government, pharmaceutical manufacturers, and the health care sector to work together to find solutions that allow for the continued use of life-saving pharmaceuticals while protecting the environment and the nation's health from unnecessary harm.

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