Pharmaceuticals as pollutants: A threat for pharmacy profession

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Introduction:

Pharmaceuticals and health care products (PHCPs) are the day to day need of common man everywhere. These substances as xenobiotics are excreted to the nature. Due to dense population and inadequate disposal of sewage PHCPs have made their way into our waters and are starting to attract negative attention. Pharmaceutical residues from humans and animals, personal care products, and their metabolites are continually introduced to the aquatic environment as complex mixtures. They can enter the water from discharge of treated domestic wastewater, treated industrial wastewater, commercial feeding operations, and surface application of manure[1]. The discovery of a variety of pharmaceuticals in surface, ground, and drinking waters around the country is raising concerns about the potentially adverse environmental consequences of these contaminants. There is increasing concern that the PHCPs detected in our nation's waters could cause adverse environmental effects, including, but not limited to; endocrine disruption in aquatic life and (or) increased antibiotic resistance.

A study by the United States Geological Survey (USGS) published in 2002 brought this issue into the limelight. A sampling of 139 streams across 30 states found that 80 percent had measurable concentrations of prescription and non-prescription drugs, steroids, reproductive hormones, and their by-products[2]. The observations are being supported by other studies detecting PHCPs in surface, ground, and drinking waters across USA are raising concerns about public safety and the potentially adverse environmental consequences of these contaminants. India and other countries of South Asia are also prone to such kind of contamination are supposed to be even more due to worse living condition, health and sanitation. However, a very few studies have been performed in this direction but situation seems to be alarming in South Asia detailed data is not available, therefore, the present discussion will be based on the data from other part of the world.

Sources of pharmaceutical contaminants:

Pharmaceutical products refer to a group of chemicals used for the diagnosis, treatment, or prevention of health conditions. Pharmaceuticals and their by-products enter the environment as pollutants in a variety of ways, including: discharge from wastewater treatment plants or private septic systems, leaching from landfills, agricultural runoff, and from local hospitals.

Pharmaceuticals do not usually persist in the environment but continuous inputs have the potential to keep concentrations relatively constant, even if at very low levels. Medications, when administered to the individual can have beneficial results, but once the active ingredients enter the environment as an unknown interacting cocktail of different compounds they can produce unwanted effects.

Pharmaceuticals initially enter wastewater treatment plants from two key sources as depicted in following figure. The active pharmaceutical compounds and their metabolites are excreted from the body; and from the disposal of unused or expired medications down the toilet or drain. If disposed of in household waste, compounds end up on landfill sites where they may enter the landfill leachate[3].

Human and Veterinary Excretion vs. Drain Disposal:

Excretion of PHCPs and/or their metabolites from humans and animals (Pets and Dairy) can vary anywhere from 0 to 100% of the active compounds. Some

compounds are almost completely metabolized before they are excreted, while others are only moderately or poorly metabolized and others yet again, such as contrast media, are excreted completely intact. The individual's diet, age, gender, metabolism, and various additional factors may play a role in the amount of metabolites produced. These metabolites may also be active compounds in and of themselves.

It is nearly impossible to determine the general ratio of pharmaceutical inputs from human excretion vs. the direct flushing of expired medication. This calculation is complicated by the vast number of active pharmaceutical compounds present, possible by-products produced through metabolism and waste water treatments, potential synergistic interactions, and incomplete drug disposal method data. Attempts to illustrate the complexity of this issue by displaying the average human excretion rates of the top drugs prescribed in 2005 are enlisted in Table 1. Each pharmaceutical is different, particularly in terms of how they behave in the human body. Virtually every drug has a different metabolic process, excretion rate, and cascade of bio-active metabolites that can complicate the picture. The list in Table 1 is driven by market share and does not take into account OTC drugs which may be sold in significant amounts.

The list only representative in nature, however, apart from them many more therapeutic agents along with ingredients and metabolite of health care products are also in use in substantial amount, their contributions are combined in the waste stream cannot be ignored. It is then difficult to distinguish the individual contributions from each medication to determine which compounds have the greatest impact.

Percent excreted obtain either from www.rxlist.com or taken from patient product inserts. The percent excreted most often equals percent found in urine though may include percent in faeces, usually in less than 24 hours. All numbers are approximate.

Occurrence and Distribution:

Pharmaceuticals in the environment, initially hormones, first came into view in the 1970's[4]. Since then scientists seem to be finding pharmaceutical compounds nearly wherever and whenever they take a close enough look. It was not until recently that researchers developed methodologies to detect these chemicals present at very low concentrations, well below therapeutic doses. The ubiquity of active pharmaceutical compounds, and the fact they are constantly and increasingly introduced to the environment as pollutants are significant to their occurrence and distribution. The nationwide United States' Geological Survey study published in 2002 found the most frequently detected compounds in surface waters were coprostanol (faecal steroid), cholesterol (plant and animal steroid), N,N-diethyltoluamide (insect repellent), caffeine (stimulant), triclosan (antimicrobial disinfectant), tri(2-chloroethyl)phosphate (fire retardant), and 4-nonylphenol (non-ionic detergent metabolite)[2]. Seven (Site 1- Merrimack River below the Concord River, Site 2- Charles River above the Watertown Dam, Site 3- Laundry Brook at Watertown, Site 4- Faneuil Brook at Brighton, Site 5- Muddy River at Brookline, Site 6- Stony Brook at Boston, and Site 7- Charles River at Boston Science Museum.) of the 139 total sites sampled in this study were in Massachusetts and of the ten most frequently detected compounds six were measured at concentrations below the national average at these sites (Table 2).

The selection of sampling sites was biased towards streams susceptible to contamination, as in dense urban areas. The high overall frequency of detection for organic wastewater contaminants, in over 80% of the streams studied was likely influenced by the design of this study

which focused on susceptible streams. most abundant contaminants as a national Table 2 displays the concentrations of the

Table 1: Human excretion rates of some drugs of 2005 by number of prescriptions dispensed.

Drug	Therapeutic Category	% Drug excreted* unchanged
Paroxetine hydrochloride	Antidepressant	< 3%
Escitalopram oxalate	Antidepressant	8%
Alprazolam	Anxiety disorders	No data available
Tramadol	Analgesic	30%
Hydrocodone	Opioid Analgesic	Very small amount
Paracetamol	Antipyretic	Very small amount
Pregabalin	Anti-seizure	90%
Oxycodone hydrochloride	Opioid Analgesic	19%
Lisinopril	Hypertension treatement	75%
Duloxetine hydrochloride	Antidepressant	< 1%
Atorvastatin calcium	Cholesterol	< 2%
Oxycodone, acetaminophen	Opioid Analgesic	8-12%
Sertraline hydrochloride	Antidepressant	14%
Metformin hydrochloride	Type 2 diabetes	90%
Venlafaxine hydrochloride	Antidepressant	34%

*Top Drug Prescription Sales for 2005 (latest year available) [Available: www.rxlist.com] (Last Visited June 12, 2007).

Table 2: Compound Concentration Comparison (Original data from USGS study)

Compound Name	Primary Use	Max (µg/L)	Median (µg/L)	MA Rivers max (µg/L)[a]	MA Rivers median (µg/L)
Coprostanol	Steroid	150[b]	0.088	4.09 (6)	0.19
Cholesterol	Steroid	60[4]	0.83	5.22 (4)	1.03
N,N-diethyltoluamide	Insect repellent	1.1	0.06	0.1 (4)	0.07
Caffeine	Stimulant	5.7	0.1	1.6 (6)	0.13
Triclosan	Antimicrobial disinfectant	2.3	0.14	0.16 (4)	0.09
tri(2-chloroethyl) phosphate	Fire retardant	0.54	0.1	0.07 (4)	0.05
4-nonylphenol[c]	Detergent metabolite	40	0.8	1[d] (7)	0.5
Ibuprofen	Anti-inflammatory	1.0	0.2	0.45 (4)	0.018
Acetaminophen	Antipyretic	10	0.11	0.94 (6)	0.009
Trimethoprim	Antibacterial	0.30	0.013	0.014 (all)	0.014

[a] River number corresponding to highest value is designated within parentheses.
[b] Concentration estimated – value greater than highest point on calibration curve.
[c] Concentrations estimated – reference standard prepared from a technical mixture.
[d] Estimated value

average compared to the streams sampled in Massachusetts. This list gives some insight into what is likely to be detectable in the MWRA system, not necessarily what is present or even biologically active. Simply because you can test for something does not make it relevant and if a compound was not detected it does not mean it is not present or significant.

Impacts and effects:

There is limited documentation regarding the direct cause and effect relationships of pharmaceuticals in the environment. The major concerns to date have been the promotion of pathogen resistance to antibiotics and disruption of endocrine systems, but many other active pharmaceutical compounds make their way into the water and have unknown consequences. To date, most of the research of pharmaceuticals as pollutants has been focused on aquatic environments. The possible effects of these substances on aquatic life are currently not well understood. Potential adverse aquatic effects in field populations are usually predicted from laboratory acute and chronic toxicity data in species such as algae, crustaceans, and fish[5]. These tests generally look at one organism's response to one particular chemical, but in the environment organisms are simultaneously exposed to a host of different chemicals over multiple generations making the extrapolation from the laboratory to the field exceedingly difficult.

Current research suggests endocrine disrupting chemicals (EDC), mainly synthetic steroids and other hormones, can lead to changes in sex ratios in fish and other aquatic organisms, "feminization" of male fish, production of vitellogenin (an egg yolk precursor protein) by male fish, and other changes that may affect reproduction or overall health[6-8]. Concentrations at which these effects were observed were lower than concentrations detected in some surface waters sampled by the USGS[2]. Aquatic environments are a major concern because organisms in this environment are subject to continual low-dose exposure[1].

With respect to pathogen resistance, the World Health Organization (WHO) warns that increasing drug resistance could significantly reduce our ability to cure illness and stop epidemics. Curable diseases, varying from sore throats to tuberculosis and malaria, may become incurable as our once-effective medicines become increasingly ineffective[9]. Possibly development of antibiotic resistance is a result of active pharmaceutical compounds present in wastewater.

For humans, consumption of potable water that may contain trace amounts of various pharmaceuticals has been identified as one of the primary potential routes of exposure[2]. While some pharmaceuticals have been measured in drinking water[10-11], a number of scientists believe that pharmaceuticals at the low levels detected do not pose an appreciable risk to human health[12]. Sensitive populations, particularly pregnant woman and children, are believed to be more susceptible to any negative effects, but studies have not shown any impacts on human health as of yet. The exposures found thus far are well below therapeutic levels for human consumption.

Because of the trace concentrations of these drugs, it would take a significant period of time, consuming approximately a gallon of water a day, to achieve a single therapeutic dose of most chemicals: consuming the equivalent of one tablet of Diazepam would take 3.5 years; a capsule of diphenhydramine 14.5 years; and one tablet of Tylenol 58 years[13]. However, the potential effects from continuous low dose chronic exposure to active pharmaceutical

compounds in humans are not clearly understood.

Solutions ahead:

It is true to say that a pharmacist is not legally bound to take any action for minimizing the pharmaceutical affluent in environment. However, as the citizen he/ she is supposed to make environment clean. In only a few countries such measures have been taken place sooner or later such actions will also be implemented in about all the countries of the world. Here we strict ourselves to the discussion pertaining to pharmacists and patient only.

Disposal of Unwanted Pharmaceuticals:

Consumer pharmaceutical wastes are created from prescription drugs for a variety of reasons, *e. g.*, a change in prescription; patient's health improves before finishing treatment, patient death, and patient non-compliance. OTC medicines are often sold in bulk and may contain more than is needed before the expiration date or the consumer may switch brands or prescriptions. Many of these expired of unwanted medications are disposed of in the trash or down the drain.

With few exceptions, countries do not have clear and consistent guidelines on how to properly dispose of unwanted pharmaceuticals, especially when it comes to the general public. In February 2007, the White House Office of National Drug Control Policy released the Federal regulations on the Proper Disposal of Prescription Drugs[14]. These general recommendations suggest unused pharmaceuticals be mixed with coffee grounds or kitty litter, placed in an impermeable bag, and thrown out in the trash. They also recommend certain drugs be flushed down the toilet. Coming in last on their list, they suggest taking unused medications to a community pharmaceutical take-back program.

Incineration is now regarded as the best disposal option for expired or unwanted medications, but it is not a commonly available option for the general public. A report[15] on how expired medications are being disposed of found that 1.4% of residents returned medications to a pharmacy, 54% disposed of medications in the garbage, 35.4% flushed medications down the toilet or sink, 7.2% did not dispose of medications, and 2% related they used all medication before expiration (See Figure 2 below).

Studies have reported that approximately one third of the total volume of pharmaceuticals sold in Germany and about 25% of that sold in Austria are disposed of with household waste or down the drain[16]. This significant contribution from private individuals turns the focus from industry to the activities, actions, and behavior of consumers on their surrounding environment. Some consider flushing unwanted medications down the toilet preferable to throwing medications in the trash where children or illicit drug users might get a hold of them, but flushing in particular may be more closely associated with causing environmental damage. By recommending the medications be crushed, combined with another substance, and placed in the trash reduces the poisoning risk but it has the potential to enter the water through land fill leaching. Even pharmaceuticals captured in leachate at lined landfills are typically transported to wastewater treatment plants, where some pass through untreated.

Prescription Drug Abuse and Poisoning:

Prescription and OTC drugs can be safe and helpful to people when used in the right way, but many can also be abused and remain a serious public health concern. Medications account for the most common poison exposure category in the United States[17]. They can cause addiction, increased blood pressure and heart rate, seizures, organ damage, and even death.

The massive number of medications available presents a substantial accidental poisoning risk if they are not properly stored or disposed. Unsecured disposal to

the garbage or using improper facilities increases the risk of drug abuse or poisoning.

Hospital Survey Summary:

In hospitals and nursing homes, pharmaceutical waste is generally discarded down the drain or land filled, except chemotherapy agents, which are often sent to a regulated medical waste incinerator. Pharmacies and drug providers usually send unused or expired pharmaceuticals back to the manufacturer, in other cases they use a reverse distribution company which disposes of the products that are non-returnable[17].

Pharmaceutical Take Back Measures:

Improper management of unwanted or expired residential pharmaceuticals poses hazards to both human health and the environment. Some medicines may enter the environment from human excretion, but others enter the environment from the direct disposal of unused or expired products through the waste water stream that could have been disposed of in a more responsible way.

In certain countries like USA, Canada, Australia, EU *etc.* take back programs provide the legal framework and the logistic resources required to allow health care facilities, patients, and the general public to return unused or expired pharmaceuticals so that they can either be reused or disposed of safely in incineration facilities. However, in India such Programme run in the goodwill of pharmacist patient relationship, no concrete legal binding has yet been imposed. Over two dozen different initiatives in USA are either studying the problem or implementing ways to solve it, including take back initiatives at pharmacies or other collection points.

Reverse Distribution:

Drug manufacturers, in an effort to encourage pharmacies or medical centers to purchase their new medications, may offer to buy back certain drugs the pharmacy or medical center is not able to sell or use. The returns industry (or reverse distribution) was created to facilitate the return of unwanted or expired medications to the manufacturer for credit. The unwanted or expired medication remains a product until the decision is made to dispose of it, therefore the pharmacy or medical distributor can potentially return them and receive credit for them without the product being considered hazardous waste[18]. Licensed reverse distributors are permitted by the DEA (USA) to handle and dispose of controlled pharmaceuticals to be sure that all controlled substances are accounted for from their creation until their consumption or destruction.

The general public does not traditionally have access to a reverse distributor for the disposal of their unwanted or expired medications and many of the services are too expensive for smaller facilities. A reverse distribution scheme for a pharmaceutical take back program executed at a local pharmacy appears ideal, but pharmacists are unable to accept controlled substances for return and are often unwilling to bother with setting up a non-controlled pharmaceutical return program due to high costs.

Waste and Drinking Water Treatment of Pharmaceuticals:

Pharmaceuticals primarily enter wastewater treatment plants from households through excretion or improper disposal, but also through inputs from hospitals and industry sewers. Existing wastewater treatment processes are optimized to reduce human waste which is primarily biological in origin, not pharmaceutical waste. Currently the major pollutants of concern in domestic waste solids are nitrates, phosphates, dissolved organic carbon, and pathogens. Treatment facilities do not traditionally monitor or measure organic microcontaminants such as pharmaceutical residues.

Influent and effluent waters can be tested for active pharmaceutical compounds, but

there are many complications. It has only been in the past few years that continually improving chemical analysis methodologies have lowered the limits of detection to allow researchers to identify these compounds and their metabolites at very low levels, particularly in a mixed waste stream matrix. Consequently, extensive extraction, cleanup, and sophisticated instrumentation are usually required to analyze these complex compounds and mixtures. Because of these advanced methodologies required, samples can only be sent to a limited set of laboratories and can often be very expensive to process.

Due to the complexity of the tests and the low concentrations present, not detecting active pharmaceutical compounds in the wastewater effluent does not necessarily mean that the water is clean and in these precise tests you only find what you are looking for. With the vast array of possible chemicals that could be present and possible interfering compounds, narrowing the range of what is to be tested for is challenging. The overall understanding of pharmaceutical removal during treatment is limited because "the analyses for these compounds are rare, and when detected, they are present at fluctuating concentrations near analytical method detection limits[19]." Most of our knowledge about the removal of these compounds is derived from the laboratory.

Wastewater discharged to sewage treatment plants is subject to various levels of treatment depending on the setup of the facility, before being discharged to receiving waters. Pharmaceutical compounds in wastewater display a broad range of removal efficiencies by waste and water treatment technologies[20]. Some pharmaceuticals are not degraded completely and travel through water treatment facilities with only minor reductions in concentrations, while other are transformed into new compounds and still other compounds may be completely degraded in the treatment process.

Other factors, besides biological treatment, affecting removal of substances from the waste stream include weather related incidents such as wet-weather overflow or the opposite, low inflow during dry conditions, which leads to higher concentrations due to a low volume of water. As a result, some portions can be directly released into the environment via wastewater effluent due to vary levels of treatment and may have adverse ecotoxicological effects.

References:

[1] Daughton, C.G. and Ternes, T.A (1999) Pharmaceuticala and Personal Care Products in the Environment: Agents of Subtle Change. *Environmental Health Perspectives*, Vol 107, Supplement 6: 907-938 [http://epa.gov/nerlesdl/chemistry/ppcp/images/errata.pdf\

[2] Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., and Buxton, H.T. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Resonnaissance. *Environmental Science and Technology*. 2002. 36, 1202-1211.

[3] Gualtero, S. 2005. Pollution Prevention Measures for Unwanted Pharmaceuticals. Columbia University web site. [www.seas.columbia.edu/earth/wtert/sofos/Gualtero_IETerm_.pdf]

[4] Tabak, H.H. and Bunch, R.L. 1970. Steroid hormones as water pollutants. In: Developments in Industrial Microbiology, Washington, pp 367-376

[5] Versteeg DJ, Alder AC, Cunningham VL, Kolpin DW, Murray-Smith R, and Ternes T. 2005. Environmental Exposure Modeling and Monitoring of Human Pharmaceuticals in the Environment. In *Human Pharmaceuticals: Assessing the Impacts on Aquatic Ecosystems*; Williams, R. T., Ed.; SETAC Press: Pensacola, FL; pp 71–110.

[6] Palace, V.P., Wautier, K.g., Evans, R.E., Blanchfield, P.J., Mills, K.H., Chalanchuk, S.M., Godard, D., McMaster, M.E., Tetreault, G.R., Peters, L.E., Vandenbyllaardt, L., and Kidd, K. 2006. Biochemical and Histopathological Effect in Pearl Dace (*Margariscus margarita*) Chronically Exposed to a Synthetic Estrogen in a Whole Lake Experiment. *Environmental Toxicology and Chenistry*. **25**: (4) 1114 – 1125

[7] Schultz, R.I., Skillman, A., Nicolas, J.M., Cyr, D.G., and Nagler, J.J. 2003. Short-term Exposure to Ethynylestradiol Decreases the Fertility of Sexually Maturing Male Trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry*. **22**: (6) 1272 – 1280

[8] Zillioux, E.J, Johnson, I.C., Kiparissis, Y., Metcalfe, C.D., Wheat, J.V., Ward, S.G., and Liu, H. 2001. The Sheephead Minnow as an in Vivo Model for Endocrine Disruption in Marine Teleosts: A Partial Life-Cycle Test with Ethynylestrodial. *Environmental Toxicology and Chemistry*. **20**: (9) 1968 - 1978

[9] World Health Organization. [www.who.int/multimedia/antibiotic_res/index.html]

[10] Stackelberg PE, Furlong ET, Meyer MT, Zaugg SD, Henderson AK, and Reissman DB. 2004. Persistence of Pharmaceutical Compounds and Other Organic Wastewater Contaminants in a Conventional Drinking-Water-Treatment Plant. *Science of the.Total Environment*. **329**: 99 – 113.

[11] Jones, O. A.; Lester, J. N.; Voulvoulis, N. 2005. Pharmaceuticals: A Threat To Drinking Water? *Trends Biotechnogyl*. **23**: 163 – 167.

[12] Schwab BW, Hayes EP, Fiori JM, Mastrocco FJ, Roden NM, Cragin D, Meyerhoff RD, D'Aco VJ, and Anderson PD. 2005. Human Pharmaceuticals in U.S. Surface Water: A Human Health Risk Assessment. *Regul. Toxicol. Pharmacol.* **42**: 296 – 312.

[13] Seiler, R.L., 2003. Chemicals from consumers. In Dasch, E.J. (ed.) Water and Science Issues. Macmillan Reference USA, The Gale Group, pp. 155-158.

[14] White House Office of National Drug Control Policy [http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html]

[15] Kuspis DA, Krenzilok EP. 1996. What happens to expired medications? A survey of community medication disposal. *Veterinary and Human Toxicology*. **38**: 48 - 49.

[16] Krummerer, Klaus. Pharmaceuticals in the Environment: Sources, Fate, Effects, and Risks. Springer. 2nd edition. 2004

[17] Bowe, Leah, Investigating Emergent Contaminants: Pharmaceutical impacts and possible solutions,

[18] 21 CFR Parts 1300, 1301, 1304, 1305, and 1307. The Definition and Registration of Reverse Distributors from the Department of Justice

[19] Snyder, S.A., Westerhoff, P., Yoon, Y., and Sedlak, D.L. 2003. Pharmaceuticals, Personal Care Products, and Endocrine Disruptors in Water: Implications for the Water Industry. *Environmental Engineering Science*. **20,** (5): 449 – 469

[20] Daughton, C.G. 2003. Cradle to Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health – Rationale for and Avenues toward a Green Pharmacy. *Environmental Health Perspectives*. **111**, (5): 757 – 774.