



GREEN PHARMA: A NEW APPROACH FOR ENVIRONMENT FRIENDLY DRUG

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ABSTRACT

Per capita consumption of pharmaceuticals is increasing globally as they play a critical role in maintaining health, but very few of us give much thought to the environmental consequences of our ever-increasing reliance on medication. After consumption, between 30-90% of the active pharmaceutical ingredients in (APIs) are excreted unchanged and enter in the environment even after sewage treatment. Active pharmaceutical ingredients are present in various spheres of the environment, because of the use of human and veterinary medicinal products. Given the complexity of the molecules that are used as active pharmaceutical ingredients and the resulting complexity in the synthesis and purification needed to produce a particular API, the pharmaceutical industry as a whole ranks low in its green practices when compared with other chemical sectors. This review focuses on the main aspects concerning environmental contamination with medicinal products, waste disposal management and towards a greener community pharmacy.

KEYWORDS: Active Pharmaceutical Ingredients (API), Environment contamination, Green chemistry, Eco-shadow, E-factor, Good Manufacturing Practices (GMP).

INTRODUCTION

The pharmaceutical industry has a substantial impact on the environment, especially when the materials and chemicals used make their way directly or indirectly into the environment. Improper disposal of unused drugs, metabolites and degraded products contaminate water and soil, threatening wildlife and human health seriously.^[2] Human male sperm count has on an average has dropped 50% since 1939, and there have been rise in infertility, genital defects, cancers (breast and prostate) and even neurological disorders among children. They also interfere with normal functioning of the endocrine system (thyroid, adrenals, ovaries and testicles), mimic hormones and seriously jeopardise reproduction, development and behaviour.

The term “eco-shadow” has been introduced to describe the ecological impact of antibiotics. They are not metabolized in human body and are therefore excreted unmodified. They are poorly degraded in nature. Presence of high concentration of antibiotics in sewage water stimulates an increased risk of selective multi drug resistant bacteria, a grave issue of global concern. This has led to some highly effective antibiotics slowly becoming ineffective. A widely used and established green metric is the E factor, developed by Roger Sheldon, professor emeritus at the Delft University of Technology in The Netherlands, which evaluates the “greenness” of a manufacturing route by its process

efficiency. The E factor is simply the mass ratio of waste to desired product. A higher E factor means more waste and a more negative environmental impact. The pharmaceutical industry as a whole has a high E factor compared with other industrial chemical manufacturing segments. The E factor for bulk chemicals ranges from 1-5, and for fine chemicals 5-50, but for the pharmaceuticals the E factor ranges from 25-100.^[1] Green Chemistry is to gear itself to address this issue not only at the formulation and manufacturing stage, but also while disposing them off without toxifying the environment. The process of minimizing the risk of such environmental contamination needs to be observed during all pharmaceutical activities (research, manufacturing, prescribing, dispensing and disposal of residual medicinal products). Increasing recognition of this problem is fuelling interest in developing new pharmaceuticals – or even re-designing existing ones to be more environmental friendly, or ‘benign by design.’ This includes drugs that are better absorbed by the human body, or the once those biodegrade rapidly in the environment.^[3,5,6]

Effect of Pharmaceutical substances present in aquatic environments on health

The disproportionate utilization of numerous types of pharmaceutical substances has increased the direct or indirect contamination of water sources and food chain. The bio persistence of these pharmaceutical remains in

water sources offer potential risks on the modification of living organism genomes and possibly long term effects on human health. Active pharmaceutical ingredients can be found in wastewater because of patients flushing down unused medicines in the toilet. Human medicine consumption inevitably leads to excretion by urine and faeces, thus increasing the levels of active pharmaceutical ingredients in wastewater. Wastewater are treated with common procedures (biological, physical and chemical) for removing contaminants, although most of the times, medicines cannot be efficiently eliminated.^[10,11] The concentration of active pharmaceutical ingredients in the environment (water) can range from ng/l up to µg/l or even mg/l (mostly in wastewater).^[4] Another problem emphasized by many

researchers is the accumulation of active pharmaceutical ingredients in the environment, which leads to continuous exposure and is more likely to produce negative effects on flora, fauna or even humans.^[7,8] Such negative effects have already been reported in literature, for example: reproductive disorders among fishes caused by estrogens, the emergence of resistant bacteria caused by antibiotics and endangering some vulture species caused by diclofenac.^[7,8,9]

Environmental studies showed the presence of various classes of medicinal substances in the aquatic system (groundwater, surface water and even drinking water) or in soil, as summarised in the table [1] below:

Table [1]: Drugs frequently found in the aquatic systems.

Type of Drug	Name of the drug
	Fluoroquinolones
	(ciprofloxacin, norfloxacin), chloramphenicol, tetracycline)
Antibiotics	Macrolides
	(clarithromycin, erythromycin, roxithromycin, lincomycin),
	Sulfonamides,
	(sulfamethoxazole, trimethoprim, sulfadimethoxine,
	sulfamethazine, sulfathiazole)
Antifungal	miconazole, fluconazole
Antiviral	acyclovir, penciclovir, lamivudine, oseltamivir
Anti-inflammatory/ Analgesic/Antipyretic	diclofenac, ibuprofen, naproxen, ketoprofen, salicylic acid), paracetamol phenazone, acetyl salicylic acid), paracetamol
Antiepileptic	carbamazepine, primidone
Antidepressants	fluoxetine, olanzapine, paroxetine
Antidiabetic	metformin, glibenclamide
Anticoagulant	warfarin
Antiemetic	domperidone
Angiotensin converting enzyme inhibitors	enalapril, captopril
Beta-blockers	metoprolol, propranolol, betaxolol, bisoprolol, nadolol, atenolol
Bronchodilator	
Diuretic substances	furosemide, hydrochlorothiazide
Narcotics and psychotropic	morphine, codeine, methadone, cocaine, 6-acetylmorphine, amphetamine, methamphetamine, 11-nor-9-carboxy-Δ-9-tetrahydrocannabinol, bromazepam, diazepam, lorazepam, lormetazepam, pentobarbital
Oral contraceptives	estrogens (17α-ethinylestradiol, mestranol)
Proton pump inhibitor	omeprazole

Sustainability and application of Green Principles in Pharmaceuticals formulation

Many pharma processes were developed in an era when waste generation and sustainability were not the key considerations. Traditional pharmaceutical manufacturing uses a “take-make-dispose” method. The pharmaceutical industry is involved in designing and manufacturing medicinal products or bioactive compounds involving chemical synthesis, a process which increases the risk of environmental water pollution. This further gets aggravated because of rejected medicines, metabolites (due to the use of various organic and inorganic solvents), disposing large amounts

of drugs in landfills and even destroying them by incineration causing disaster to the environment.

“Green chemistry” refers to the promotion of safe, sustainable, and waste-minimizing chemical processes. In 1998, Paul Anastas and John Warner co-authored a book setting out the 12 principles that form the basis of green chemistry.^[12-15] including a range of ways to reduce the environmental and human impact of chemical production. Green chemistry gives innovative scientific solutions, applies to life cycle of a chemical product, including its manufacture, use, design, and ultimate disposal reducing the negative impacts of

chemical products on environment and human the health as summarised in table [2].

Table [2]: Important Principles of Green Chemistry.

Principles of Green Chemistry		
1	Prevent waste	Designing chemical synthesis to avoid waste. Reduce the waste production as much as possible. Do not leave the waste to be treated.
2	Maximize atomic economy	Designing the synthesis in such a way that the final product contains the maximum percentage of the initial material. Little or no atom is wasted.
3	Design less dangerous chemical synthesis	: Designing the synthesis that either use, or generate substances with minimal or no toxicity for humans or the environment.
4	Design safer chemicals	Designing chemicals which are fully effective but have minimal or no toxicity.
5	Use safer solvents and reaction conditions	Avoid the use of separating agents, solvents or other auxiliary chemicals. If required, use the safer ones.
6	Increase energy efficiency	Perform chemical reactions at room temperature and pressure whenever and wherever possible.
7	Use renewable raw materials	Use initial materials which are renewable rather than exhaustible ones. Renewable raw material sources are usually agricultural products or other bio-waste or waste from other processes; sources of exhaustible raw materials include the fossil fuels (oil, natural gas or coal) or mining activities.
8	Avoid chemical derivatives	Avoid the use of any temporary changes or protective groups, if possible. These derivatives use additional reagents and generate a lot of, often avoidable, waste.
9	Use catalysts, stoichiometric non-reagents	Minimize the waste by using catalytic reactions. Catalysts are very effective in smaller quantities and can perform a single reaction multiple times. They are preferable over the stoichiometric reagents, which are required in excess and can react only once.
10	Design chemicals for degradation	Design those chemicals which reduce harmful substances after their use so that they do not accumulate in the environment.
11	Real-time pollution prevention	Include an in-process control and monitoring, in real time during the synthesis to reduce or eliminate the formation of harmful by-products.
12	Minimize the risk of accidents	Design such chemicals with their physical forms (solid, liquid or gaseous) to reduce the potentials of chemical accidents including fires, explosions and releases into the environment.

The biggest challenge now is to gear towards sustainability through the collaborative efforts of Industry, academic institutions, environmental groups and government to minimise the use of natural resources (energy, water etc.) with green innovations and environmentally benign products and to translate green principles into measurable goals for environmental sound research, development and production. This might thrive a drive to adopt “greener” methods, less toxic reagents and solvents, minimising effluents and solid waste, drug recycling and reduction of waste from households giving hope to mitigate the damage and even to change course for future research.

Biocatalysis and enzyme catalysis (Green Chemistry) are in great demand these days and their application in chemical manufacturing is very promising. Enzymes are biomaterials that can biodegrade under environmental conditions. They are considered as alternate and

renewable chemicals and are cost effective for the pharmaceutical industry. Furthermore, because enzymes rely on specificity, they can synthesize complex structures with high levels of regio-, chemo-, and stereo-selectivity and have the advantage of cutting down the number of steps in an organic reaction and thus producing cleaner products with scant requirement for purification. Advantages of different green processes used in drug manufacturing are given below in table [3].

Table [3]: Advantages of common Green processes used in drug manufacturing.

Drug	Commonly used for	Changes acquired in the process	Benefits
Atorvastatin	Lower cholesterol level, prevent heart disease	Use of enzymatic catalysis process	Economical Environmental friendly
Doramectin	Veterinary Drug for treating gastrointestinal roundworms, lungworms	Use of biocatalyst	Increased efficiency of reaction Minimizes waste generation Minimizes by-product production
Gemifloxacin	Antibacterial Bronchitis and pneumonia caused by bacterial infections.	Use of biocatalysis process	Time saving Energy efficient Reduced waste products
Ibuprofen	Pain Killer	Atom economy reduction of process step	Minimum waste production Lesser by-products
Pregabalin	Anticonvulsants, Analgesics treat epilepsy and anxiety	Replacing chemical by water	Energy saving Minimized use of chemical
Sertaline Hydrochloride	depression, panic attacks,	Greener method for commercial production	Increased yield of the product Energy saving Water saving
Simvastatin	Lower blood level, LDL Reducing heart attack;	Use of low cost feedstock Use of enzymatic chemical process	Higher yield Environmentally safe production
Sitagliptin	Treat High blood Sugar	Use of Enzymatic process	Improved yield Replacement of Metal catalyst Minimum waste produced

Guidance on WHO Good Manufacturing Practices (GMP) for pharmaceutical products containing hazardous substances

Growing antimicrobial resistance linked to the discharge of drugs and particular chemicals into the environment is one of the most worrying health threats today. It is only recently that the need to address waste and wastewater management from pharmaceutical production has been explicitly addressed. WHO gave the following options and tools to reduce and mitigate the uncontrolled disposal of waste and wastewater containing antimicrobials while manufacturing medical products.^[16] It directed Regulatory bodies that are responsible for enforcing environmental protection standards and waste/waste water management in all Member States; consistent with a multidisciplinary approach, the Ministries of Health, Ministries of Environment or Pollution control boards and Ministries of Agriculture, as appropriate.

According to these guidelines,

- Facilities should be designed and operated in accordance with the main GMP principles, to ensure quality of product; to protect the environment and the public from possible harmful effects of products containing hazardous substances.
- The risk assessment should also determine that which phases of the product, production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

- As the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.
- If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.
- All effluent should be disposed of in a safe manner and the means of disposal should be documented. Where external contractors are used for effluent disposal, they should have certification authorizing them to handle and treat hazardous products.
- Sewage, refuse and other waste (e.g. solids, liquids or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.
- Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.
- Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection point

Awareness and prudent use of pharmaceuticals

Self-medication, storing excessive stocks of medicinal products at home, polytherapy, patient noncompliance to medication and adverse effects are factors that can lead to the accumulation of unused or expired medicines and

consequently their improper disposal, making patients also responsible for environmental contamination.

Patient education regarding the rational consumption of medicinal products and the proper disposal of unused or expired medicines should be imparted through information campaign and take-back programs, also named as pharmaceutical-return programs.^[17]

Community pharmacies can be formulated to help reducing the impact pharmaceuticals can have on the environment and preventing unnecessary waste. At the same time, they can make a meaningful difference in contributing to a healthier planet by integrating sustainability policies within their daily practice.^[18]

- Running safe Medicine disposal campaign on social media.
- Expired or unused medicines can be returned to their community pharmacy.
- Pharmacists should encourage return of expired and unused medicines and prevent the inappropriate use or reuse of medicines.
- Actively participating in collection schemes and campaigns for returning unused and expired medicines where appropriate.
- Adopting effective waste collection policies for the compounding of medicines in pharmacy practice.
- Collaborating with prescribers to encourage the rational prescription of medicines aimed at preventing leftover medicines as much as possible.
- Advising patients on the availability of 'greener' medicines where such information is available.
- Supporting patients with therapy adherence during consultations and the provision of structured pharmacy services.

Encouraging and Adopting environmental-friendly procedures

- Providing bags to patients made of recyclable materials only where possible and where needed.
- Reducing plastic waste overall in pharmacies and help raising awareness on unnecessary single use packaging towards wholesalers and manufacturers of medicines.
- Adopting environmental-friendly procedures related to procurement and distribution processes, including home deliveries of medicines.
- Making use of renewable energy sources as much as possible.
- Encouraging environmental-friendly commuting of pharmacy staff.
- The environmental impact of pharmaceuticals can be reduced through a systematic decrease in the use of pharmaceuticals that have a disruptive effect on the environment
- In addition, the pharmaceutical industry needs to design technologies for manufacturing a “**greener pill**” that can have a therapeutic effect in the right dose at the right place and can still be eco-friendly.

Role of Doctors in reducing pharmaceutical pollution

Doctors can control the duration and dosage of individual prescriptions, and are well positioned to help reduce the risk for accumulation of unused pharmaceuticals that become waste and can end up in the environment. **Pharmacogenomics** represents a new field in personalized medicine that can support physicians in prescribing a more efficient, safer and rational medicinal therapy. Further they can do by Suggesting lifestyle changes measures (diet, exercises etc.) before prescribing medicines.

- Prescribing environment friendly medicines wherever possible.
- Prescribing antibiotics prudently.
- Antibiotics as far as possible should be given in tablet form instead of intravenously in the blood, in this way reducing the doses that get into the environment.
- Getting information about the environmental impact in the preparation of the particular drug, its degradation speed and the API present in it from the pharmaceutical companies.
- Reminding patients about the safe disposal of unused medicines. Advising patients to never dispose of unused pharmaceuticals in the toilet or sink.
- Physicians should also focus on reducing polytherapy.
- By verifying the pharmacokinetic profiles of medicines in order to select the ones that are easily and highly metabolized, etc.
- In order to optimise the use of pharmaceuticals and at the same achieve better health and a better environment, doctors are experimenting with a “*physiotheque*”. Here, instead of pharmaceuticals, patients are prescribed exercise, e.g. dancing, city walks, using walking poles and similar activities.

Proactive role of Individuals

- Don't pick up a prescription unless you are going to use it, except for an emergency medicine you should have on hand.
- Talk to your doctor about lifestyle medicine, which focuses on healthy habits.
- Regular exercise and eating healthy food can prevent disease and promote longevity.
- These lifestyle changes can help reduce or eliminate the need for medications.
- Do not put medications down the toilet or sink.

Health care is a partnership, and with thought and care, we can work together to have the best of both worlds — a healthier you, and a healthier planet.

CONCLUSION

Pharmaceutical industry came as a boon for the humanity solving the myriads of the health problems mankind faced. But, in the indiscriminate pursuance of excessive commercialisation and consequent profits, this boon

veered its trajectory to a dangerous domain. While tackling major health issues medicines do cause some side effects and residual consequences. On the one hand pharmacological molecules were created to address specific health scare, but the lack of purity of process generated many more toxic molecules as by products. Disposing these residual molecules has been a huge challenge before health monitoring agencies. Green Chemistry with its thrust on *purity of process* has its task clearly cut out to minimize such undesirable chemical by-products in pharmaceutical industry. To have an effective strategy all stakeholders, from scientist to manufacturer to regulator to policy planner to doctors and the patients, have some proactive roles to play. A composite plan with long term sustainable future needs to be evolved to stop this boon turning into the curse.

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