The Emerging Environmental Burden from Pharmaceuticals

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The enormity of pollution due to pharmaceuticals in India has caught the attention of researchers all over the world. This was due to the near extinction of vultures in the Indian subcontinent in the 1990s caused by diclofenac and a recent study in 2007 by Swedish scientists on pharmaceutical effluents in Patancheru in Hyderabad. The massive outsourcing of pharmaceutical production by the west has made third world nations like India a victim of unbridled opportunism. As the west wakes up to the environmental implications of “pharma pollution”, Sweden’s Medical Products Agency recommends a reduction in outsourcing and revisions in pharma manufacturing practices. Would these exhortations reduce pharmaceutical pollution in India or would they adversely impact India’s advantages in the global drug market?

Nobody ever anticipated prescription drugs to pollute the world, except perhaps at the point of manufacture. Pesticides were the only recognised environmental pollutants employed in healthcare. The menace of pollution from the use of dichlorodiphenyltrichloroethane insecticide (DDT) began to be appreciated only in the late 1960s and eventually culminated in its ban in the United States (US), as late as in 1972. Until recently, prescription drugs were thought to be environmentally benign, owing to the relatively small manufacturing volumes and the extensive safety guarantees associated with the licensing.

In the early 1990s, the Indian subcontinent witnessed a dramatic reduction (approximately 95%) in the population of its vultures. Ten years later the culprit was identified as diclofenac (an anti-inflammatory drug). Vultures feeding on dead cattle, dosed with veterinary formulations of diclofenac, died en masse on account of kidney failure (Oaks et al 2004). This is the first recorded event that linked prescription drugs with the extinction of a species. This being a recent phenomenon, the possibility of drugs polluting the world remains largely unknown, even among the educated.

If the extinction of vultures sounded like the first warning bells about pharmaceutical hazards of the environment, the second trigger, which came from a report by Swedish scientists, took the world by storm. From effluent samples collected from Patancheru (a Hyderabad suburb; the world’s pharmaceutical manufacturing hub), the Larsson study (2007) identified a number of drugs in alarming quantities. Among the 59 active pharmaceutical ingredients (API) tested, 21 were detected at levels greater than 1 microgram/L. More than 11 drugs were detected at the highest level ever on the planet. Waste water from Patancheru showed 150 times the highest levels of pharmaceuticals detected in the US. Ciprofloxacin (an antibiotic), generally detected at microgram levels per litre in the west, was detected at 31 mg/L in Patancheru effluents (this is much greater than the maximum therapeutic blood level). The discharge load of ciprofloxacin has been estimated to be greater than 45 kg per day. The antibiotics lomifloxacin, ofloxacin, norfloxacin, etc were detected at levels which are toxic even to plants and algae. It was estimated that if the drugs extracted from the effluents were sold as tablets, it would fetch approximately Rs 65 lakh per day (Larsson et al 2007).

Scale of the Environmental Burden
Drugs are considered among the most non-biodegradable in the environment (Stuer-Lauridsen et al 2000). Most drugs, being insoluble in water, are not effectively washed away by rain. Therefore, drug residues tend to build up in the environment and eventually accumulate in the bodies of terrestrial and aquatic organisms (Halling-Sorensen et al 1998).

Many drugs not only resist their own degradation, but also interfere with the microbial degradation of other substances in sewage. This is because antibiotics kill friendly microbes which decompose organic waste. Another major concern is that microorganisms exposed to extraordinarily high concentrations of antibiotics evolve into extremely dangerous pathogens. The competitive struggle for survival in effluents containing a cocktail of antibiotics would eventually favour the selective survival of the deadliest microbes resistant to many antibiotics (Kummerer 2001). This has already resulted in the emergence of many multi-drug resistant microorganisms in effluents exposed to environmentally-relevant levels of antibiotics (Larsson et al 2007). Microbial resistance to antibiotics is a global concern because jet travel promotes the rapid spread of epidemics. Thus, pollution anywhere becomes a problem everywhere.

Waste water effluents may be from three different sources – municipal, industrial and hospital (Tsoumanis et al 2010). Incomplete metabolism, improper disposal or insufficient removal by the...
treatment plants are the main causes for the release of pharmaceuticals into the environment (Bergheim et al 2010). Even small quantities of drugs can potentially harm aquatic life (Bound and Voulvoulis 2005). For instance, ethinyl estradiol (a hormonal drug) found in effluents, has resulted in feminisation of fish downstream of sewage plants (Larsson et al 2007). Effluents from Patancheru Enviro Tech Ltd (PETL), Hyderabad, India, produced up to a 40% growth reduction in tadpoles, even at very low drug concentrations (Carlsson et al 2009; Fick et al 2009). Even at very high dilutions, pharmaceuticals in effluents stimulated expression of genes (Gunnarsson et al 2009; Kristiansson et al 2011).

Even the most developed countries are not entirely free from the environmental burden of pharmaceuticals. Even in developed countries, pharmaceuticals have been detected in surface, ground and drinking water (Fram and Belitz 2011). The Associated Press reported that traces of pharmaceuticals have been found in drinking water supplied to around 4.6 crore Americans (Larsson et al 2007).

Excretion via urine and faeces is the primary route by which drugs enter the environment (Daughton and Ruhyo 2009). Antibiotics have been detected in livestock and hospital effluents (Sim et al 2011). Although separate treatment of hospital waste water would reduce API load, it may not reduce high-risk APIs because faeces and urine are also sources of API (Escher et al 2011). Drugs discarded in municipal solid wastes and dumped in landfills could undergo degradation, adsorption, or leach into waterbodies. A study reported drugs at levels of 7.4 to 45mg/kg in solid waste (Musson and Townsend 2009). Municipal waste water treatment plants are an abode of antibiotic-resistant bacteria (Novo and Manaia 2010). Even well regulated drugs such as narcotics have been found in significant quantities in rivers, waste water treatment plants and hospital effluents (Lin et al 2010).

Unused prescription drugs, which accumulate as a result of altered disease states, missed doses, changes in prescription, expiry, etc are often discarded unscientifically (Thormodsen et al 1997). Popular routes of disposal such as garbage, toilet, sink, etc, result in significant environmental burden (Bound and Voulvoulis 2005).

Pharmaceuticals having multiple uses have a greater propensity of polluting the environment. Antibiotics are routinely used as feed supplements in poultry, fish or pig farms. Pig house dust was found to contain five antibiotics in a combined concentration of 12.5mg/kg (Hamscher et al 2003). In a recent study in the US, pigs given low doses of antibiotics had gut bacteria that were resistant to antibiotics, confirming that the routine practice of feeding antibiotics to livestock leads to emergence of antibiotic-resistant bacteria (Looft et al 2012). The evolution of the methicillin-resistant staphylococcus aureus (MRSA), also known as pig MRSA or livestock-associated MRSA, which infects people with direct exposure to livestock, has also been traced back to antibiotic use in livestock (Preidt 2012).

The West Is Waking Up
India pays scant attention to pollution. Around 70% of all available water in the country is polluted; 7.3 crore working days each year are lost due to waterborne diseases. India has also earned notoriety with the intractable multidrug resistant New Delhi metallo-beta-lactamase-1 (NDM-1)-producing superbugs, being named after the Indian capital (Kumarasamy et al 2010). The alarm bells sounded by the Larsson study (Patancheru disaster) is probably responsible for triggering worldwide research on pharma pollution. India can take “credit” for having provided two samples of calamity (vulture extinction and Patancheru) for the world to study.

Andhra Pradesh accounts for 80% of the drugs manufactured in India. However, the Indian pharmaceutical industry is highly fragmented with approximately 34% of the total market share being accounted for by the top 10 companies and more than 1,300 companies supplying the rest. PETL, Hyderabad, for instance, receives about 15 lakh litres of waste water/day, from 90 bulk drug manufacturers. The clarified effluent is finally discharged into streams which merge with Godavari and solid waste is used as landfill (Larsson et al 2007). The Patancheru disaster was inevitable because smaller companies have very inadequate effluent treatment plants.

Many pharmaceutical firms are migrating to the greener terrains of Himachal Pradesh, Punjab, etc to enjoy tax concession; further expanding the reach of pollution. In Toansa Village (Punjab), groundwater has been found polluted up to 100 feet depth (Ghosh 2006), highlighting the implications of pharma migration to greener terrains.

The US introduced federal guidance for disposal of prescription drugs in February 2007. It recommends discarding unused pharmaceuticals to household trash, after mixing the pharmaceuticals with an inert substance and concealing the contents from view. Following the Montreal protocol-1987 (Leach 2007), US Food and Drug Administration (FDA) is currently phasing-out chlorofluorocarbons (propellant in inhalers) and replacing it with alternatives which do not deplete the ozone layer. The US FDA’s recent order to restrict antibiotic cephalosporin in livestock production is expected to contain the spread of drug resistance (Levy 2012).

In the west, hospitals follow scientific safety guidelines for the appropriate sorting and disposal of unused/expired drugs (Faure and Rizzo Padoin 2003). Prudent options such as community, city, and state collection events, government-funded projects, etc are also being offered (Glassmeyer et al 2009). Sweden recommends return of unused medicines to a pharmacy. Patient education at least partly remedies the problem of unscientific drug disposal (Seehusen and Edwards 2006). A formalised protocol for drug disposal and destruction worldwide has become essential today (Tong et al 2011). However, many countries including India have no standard medication disposal protocols yet.

Opinion is divided on donating unused prescription drugs. Donations can often cause harm because such drugs may have expired or lack prescribing information.
World Health Organisation says storage and handling of unused drugs is a strain on resources, pose logistical bottlenecks and create environmental hazards (Gold 1995). Reports suggest that unused drugs and human excreta should be treated as chemically hazardous waste (Mayer 1992). This policy may not be a good idea for poor countries like India.

**Apathy towards Pollution in India**

Pollution has never been a major concern of the public administration in India, except when there is a public outcry. The enormity of pharma pollution began to get noticed with the Larsson study. Experts had already recommended a policy shift from pollution control to pollution prevention (Kathuria 2001). However, the timing of creation of the Environment Cell under the department of pharmaceuticals linked to the Ministry of Environment and Forests (MoEF), in November 2008, suggests that the Larsson study was the triggering event.

In India, industrial effluents are handled by end-of-pipe treatment, which, like common effluent treatment plant, results in residual persistent organic pollutants and toxic metals in the treated water. The common treatment of effluents from heterogeneous industries results in a mixture of chemicals with unpredictable toxicology (Kathuria 2001). The antibiotics in the effluents can kill the very same bacteria that breakdown toxic wastes.

The near extinction of vultures led to a ban of veterinary formulations of diclofenac in 2006. However, a survey (November 2007 to June 2010) revealed that 36% of 250 veterinary and general pharmacies in 11 Indian states continued to sell veterinary formulations of diclofenac. Moreover, 30ml vials of diclofenac intended for human use are being sold for veterinary use. Only Jharkhand has seen some rise in vulture population due to increased awareness from continuous media campaigning (Sudhi 2011).

**Globalisation to Blame?**

The Hatch Waxman Act (Mossinghoff 1999), which promoted generics, has led to the outsourcing of pharmaceutical production to third world nations like India and China. Globalisation and outsourcing has made India a major producer, meeting 40% of world’s and 90% of domestic drug needs. This highly knowledge-intensive industry is expected to grow at a rate of 21% by 2013-14. Cygnus Business Consulting and Research estimate that by 2013, India will be the second largest bulk drug manufacturer in the world (Peethambaran 2011).

Around 31% of drugs in the Swedish drug market originate from India. Financial reasons now dominate environmental concerns. The high growth in volumes of pharmaceuticals has brought in its wake, concerns about the environmental burden of pharmaceutical waste. The Central Pollution Control Board and the MoEF has ranked pharmaceutical industry as one among the 17 highly polluting industries in India.

Outsourcing of production to low salary countries is an attractive option for the west, and is good business for both the parties concerned, but at the cost of the environment (Larsson and Fick 2009). In effect, the west is exporting their environmental problems to India. The lack of awareness on the API source is a major reason for the west ignoring the implications of outsourcing. “We have no reason to believe that the market situation, and thus the ethical responsibility, is markedly different in other western countries” (Larsson and Fick 2009: 162).

Green chemistry minimises by-product waste and replaces the worst reactions with green technology. Non-biological methods using ozone, \( \text{UV} + H_2O_2 \) or activated carbon, etc, are better for treating antibiotic-containing effluents (Larsson and Fick 2009). Many routine chemical reactions in pharma manufacture can be replaced with green but expensive alternatives. Pharma giants win awards for their innovations in green technology but outsource their production to India. Unbridled free market capitalism is forcing companies to cut costs at the expense of the environment.

China’s biggest antibiotics producer has been accused of releasing effluents with 10 times the admissible limit of chemical oxygen demand. However, the Chinese pharma companies enjoy government support while pollution is taking away India’s competitive edge in APIs. The small-scale industries in India need Rs 3-4 crore for effluent treatment alone. The cut-throat competition could eventually destroy the competitive advantage of Indian pharma.

Pharmaceutical Research and Manufacturers of America, representing major US drug makers, said “we cannot comment about Indian pollution because Patancheru plants are making generic drugs and their members are branded”. Generic Pharmaceutical Association said “issues of Indian factory pollution are not within the scope of the activities of our group”.

Environmental pollution should be an internationally shared responsibility. The massive outsourcing of pharmaceutical production, owing to globalisation, has made India a victim of unbridled capitalistic opportunism.

**Concluding Remarks**

Every pill eventually ends up in the environment. Around 95% of the antibiotics are excreted unaltered (Boehringer 2004). Approximately 54% of people throw medicines into trash (Choi 2007). The general water treatment plants are ill-equipped to handle pharmaceuticals. Thus, “drugs pollute the world twice, firstly in the bodies of those who take them and secondly, in the rivers and oceans where the toxic residues inevitably accumulate” (Adams 2009).

The diclofenac and the Patancheru episodes have their origin in India and have served as critical landmarks that exposed the scale and scope of a hitherto unknown phenomenon called pharma pollution. Both these events highlight the pivotal role of academics as whistle-blowers. The proactive role played by academics further emphasises the need to involve them while framing policies in manufacture and prescription of medicines.

The 71st International Pharmaceutical Federation (FIP) World Congress in Hyderabad, India, in September 2011 engaged a special session on the environmental implications of pharmaceutical manufacture (Unnikrishnan 2011), in which a team of Europeans, regretted the
situation emerging in the third world. Sweden’s Medical Products Agency Report recommended reduction in outsourcing and good manufacturing practices (GMP) revisions to control emissions (Taylor 2011). The new European Union regulations would have to specify and prioritize proven hazards, e.g., antibiotics and hormone disrupting agents. The proposed revisions in GMP are a warning note to the API exporters of the third world.

NOTES


2. New Delhi metallo-beta-lactamase-1 (NDM-1) enzyme producing bacteria, resistant to beta-lactam antibiotics, was first detected in a Swedish patient of Indian origin in 2008.

3. FDA and the White House Office of National Drug Control Policy (ONDCP) developed the first consumer guidance for proper disposal of prescription drugs, accessed on 13 December 2011: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm301653.htm


REFERENCES


