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DRUG MANUFACTURING RUSH AND ENVIRONMENTAL PRESSURE IN INDIA; NEED TO ADDRESS ITS OWN WASTE

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ABSTRACT

Modern medicine is incomplete without antibiotics, which are used worldwide to treat serious illnesses, complex surgeries, and common ailments. The production of antibiotics and the management of waste and wastewater which is an inevitable part of the whole supply chain is a problem that can be given due importance. There is an urgent need for greater encouragement to strengthen compliance, address gaps in laws and regulations, hold pollution control boards accountable, enforce regulations and spread greater public awareness and policy for patient, community and environmental safety.

KEYWORDS: antibiotics, toxicity, pharmaceutical industries, environment, discovery.

INTRODUCTION

Medicines are thought to reach the environment primarily through improper use or disposal. Although concentration of pharmaceuticals excreted by humans in the environment is limited because the prescribed dose is given to only a fraction of the population. In contrast, recent research has identified direct outbursts for drug production as a source of high-level environmental emissions that, in some cases, far exceed the concentration of toxic limit. Risk management also varies between production and naturalization in terms of accountability, profit creation, legal opportunities, replacement opportunities and costs. Medical waste is probably made from a combination of titles at a health care facility, including but not limited to IV preparations, standard combinations, fractures, used ampoules, needles, and IVs, unused preparations, fallow unit doses, personal medications and expired medicines.

Various production areas are found to be sources of higher environmental pressure than those caused by drug use. Drug manufacturing plants produce a lot of waste during production, housing maintenance and operation. Various categories of drugs have been labeled as environmental pollutants such as analgesics, antibiotics, antiepileptic, antihypertensive, antiseptics, beta-blocker heart drugs, contraceptives, hormones, and psycho-therapeutics. Pharmaceutical products are used in human and animal medicine and are a stage of emerging pollutants. Antibiotics are widely used, but research shows that up to 95% of antibiotic chemicals are released unchanged in the sewage and effluent. This is one of the major sources of bacterial resistance against antibiotics. Microbial population and food chains are getting affected because of high concentration of antibiotic discharge.

The weak point is that toxic substances are tested from what is known as human toxins rather than from unexpected potentials. Industrial institutions are still under the network of drug control and pollution control; however, Educational Institutions do not have such controls. Therefore, there is no limit to the research that can be done in educational institutions.

In this age of the booming pharmaceutical industries there is also an increase in competition, but this competition must be managed in the right way without harming the environment.

Here, we review studies about industrial and academic drug discovery rush and emerging environmental pressure.

Environmental Consequences of Pharmaceutical Contamination

Ecosystems exist in a fine balance; disturbances can lead disastrous consequences and create a surge of knock-on effects.

Academic Institutions

Lack of governance

Most industries are governed by various agencies and policies as set out in Schedule M; which is part of the Drugs and Cosmetics Act 1940 and contains information on good production practices, quality control system and other related topics. Good laboratory practice aimed at ensuring the quality and integrity of non-clinical laboratory studies dedicated to support research.

This type of management does not exist in educational institutions and research labs. Much research takes place in educational institutions and any new concept is aimed directly at

patenting without being reviewed in research labs or industries. A good flow of new findings or ideas should be from the educational industry to research labs to the industry. If the discovery is significant and novel it can be referred to a patent so that it could be available in the market.

No limitation and irrational design- As there is a lack of governance there is no limit to the amount of research conducted in research laboratories and educational institutions. No specific or specified objectives will be available most of the time. This leads to an increase in irrational and unconventional research methods and a waste of time if research does not produce results.

Lack of monitoring- There is a lack of oversight in equipment and the number of chemicals used in labs and educational institutions, no one keeps a proper check on the chemicals used which often leads to increased research and leads to waste of resources. While, in industries proper monitoring of research and the number of chemicals and equipment used are maintained.

Pharmaceutical Industries

The Indian pharmaceutical industry today is at the forefront of India-based industries with a wide range of capabilities in the complex field of drug manufacturing and technology. To meet the demands of research, multinational companies have to their own in-house or separate R&D unit. New drug development requires consortium approach of specialized personnel in field of physiology, pharmacology, toxicology, chemical engineering and pathology. As a result of this diversity of research and development in medicine, large amounts of chemical and biological waste are produced. The various sets of waste streams make the waste naturally complex which creates a treatment problem. Research and Development (R&D) division in the pharmaceutical industry includes chemical research, microbiological research and pharmaceutical research. From this a large quantity of chemical and biological waste is produced and a report on R&D drug waste is rarely available.

International authorities such as the Food and Drug Administration and the European Medicines Agency strictly regulate drug supply chain in terms of drug safety but environmental standards are not enforced. Drug manufacturers must adhere to the Good Manufacturing Practices guidelines - but those guidelines do not specify pollution (Brown A 2019).

Contaminated water from the production of antibiotics is a major source of antimicrobial resistance. The concentration of antibiotics in effluents from antibiotic production areas can reach alarming levels. One Indian wastewater plant, which receives waste from ~ 90 drug manufacturers, 45 kg of ciprofloxacin is released into a nearby river each day. As a comparison, the total daily consumption of the whole country of Sweden, is 9 kg. In addition to the obvious dangers of toxic effects on living organisms such as these antimicrobial particles, it has been shown that genetically resistant strains were ameliorated in river water.

As antibiotics are transported through water which results in the formation of antibiotic gradients. Even very low antibiotic concentrations may be sufficient to select the most resistant bacteria, and it has been shown to be the case at least in the laboratory (Finley RL et al. 2013). Most of the world's leading drug manufacturers and generic companies Aspen, Aurobindo, Cipla, Dr Reddy's, Fresenius Kabi, Lupine, Macleods, Mylan, Sun Pharma and Teva that make medicine for National Health Service (NHS) and other health systems fail to disclose antibiotic discharge from factories. There are only a few manufacturers who follow the limit of discharge in waste water.

Pharmaceutical companies have a clear responsibility to address the contamination of their supply chain, not only just because of human health is associated with untreated waste from pharma production but also to control development of drug-resistant pathogens. Antibiotic waste from the production of pesticides in the environment is a neglected driver of antimicrobial resistance. In 2017 the Bureau of Investigative Journalism reported on a study revealing extremely high levels of antimicrobials - as well as superbugs - in contaminated water from a large drug production facility in the Indian city of Hyderabad (Davies et al 2018). Even the leading mainstream companies have shown no evidence of a plan to reduce the impact of antibiotic production on the environment as reported by the Antimicrobial Resistant Benchmark 2018. There are only two companies - GSK and Novartis - that monitors their external waste disposal plants to follow their limits. Others are not looking at outsourcing by their external waste management centers, the report said.

While we will also need to develop new antibiotics in the future, we cannot focus on this approach as a solution. New drugs take time to develop, be tested and approved before they are available to patients. If we do not react to these behavioral changes, we will continue to encourage bacteria to build resistance to new viruses in the future. Without taking a closer look at the environmental dimensions.

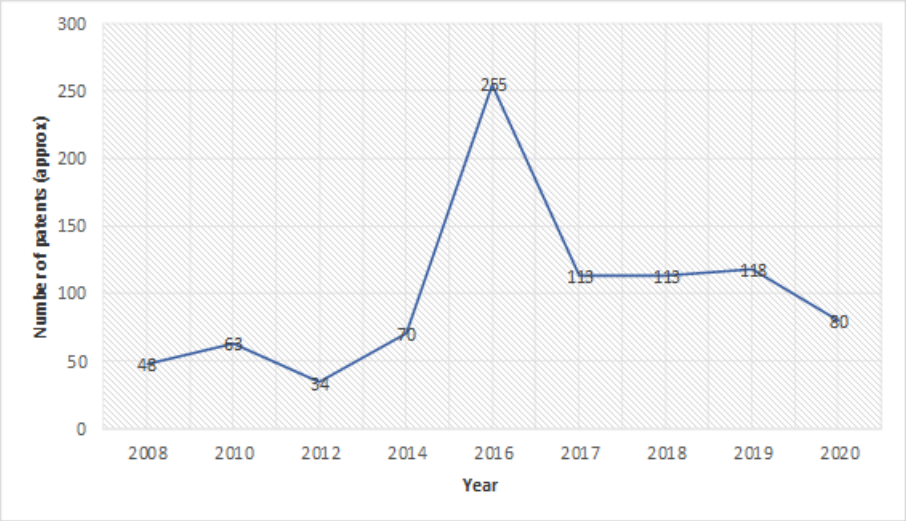

Fig 1: Number of antimicrobial patents and patent applications filed in years 2008-2020.

This graph represents the number of patents and patent applications filed in the antimicrobial sector from 2008 to 2016. This information was obtained from the official Indian Patent Office Journals and was developed for their corresponding year. The number of patent cases represents the amount of research conducted in the antimicrobial field. With this we can also see an increase in the value of ownership over the past three years. The reasons for this could be an increase in drug resistance or an increase in government funding for the field of scientific research. In addition, the research conducted is not limited to these values, as there will certainly be innovations and discoveries that have not been patented. These research papers form a large database of non-copyrighted documents. This rise in unsupervised research has led to a state of emergency without finding the desired results.

Possible Solutions

Regulatory needs

Environmental emissions need to be controlled.

• Ensuring adequate information and transparency on the effects of natural remedies.

• Ensuring adequate and reliable assessment of the natural risks of drug interventions.

• Prevent the natural release of therapeutic drugs throughout their lives.

• Controlling the release of drugs in an environment where prevention is not possible.

Indian scenario as far as compliance is concerned?

Since India and China are leading producers, they need to enforce strict procedures. The number of compliant producers is small, most of them non-compliant, thriving under weak

enforcement and dumping of waste in public water rivers such as lakes, rivers and bodies of water.

There are several hundred manufacturers of APIs (active pharma ingredients), which produce only a small percentage of compatible ones. Compliance here refers to effective waste management, following good production practices, following guidelines issued by the waste and state boards. Manufacturers do not have or treat waste plants because of the costs involved. Government departments are also based on tender processes that prioritize costs rather than have long-term implications. Weak enforcement and current legal gaps only exacerbate the problem. Today, most of the raw materials and links of antimicrobials are made in China and India (80- 90%). Therefore, these countries have a great responsibility to contribute to the resolution. In recent years, we have seen a growing number of product recall and import restrictions initiated frequently by the US Food and Drug Administration (FDA) or the European Directorate for the Quality of Medicines and Health Care (EDQM) (Nautiyal 2016). If we follow the precautionary principle that "when an activity raises threats to the detriment of human health or the environment, precautionary measures should be taken even if the other causes and relationships are not scientifically proven.

International authorities such as the Food and Drug Administration and the European Medicines Agency strictly regulate drug delivery mechanisms - Environmental standards should also be included in their regulation. Drug manufacturers must adhere to the guidelines for Good Productivity - those guidelines include pollution control. Having proper government control in various industries and disciplines. Limits the number of tests.

Proper monitoring should be done in all facilities and labs as it is done in the industry. Building materials should be carefully inspected to prevent them from being wasted. Rational designing of drug formulations and developing automated software for proper validation of the filed patents.

Public Awareness

Details on the environmental impacts of APIs are not available to the public or authorities. Availability is usually limited to disaster risk assessors only.

Raise the community's sense of commitment to the environment by showing how their actions as individuals contribute to the impact of pharmaceuticals on the environment.

Managing risk

Some of the leading Multinational pharma industries such as AstraZeneca, Novo Nordisk, effectively manage waste from, then recycle and recycle things where possible when they produce waste. Novo Nordisk's new environmental strategy is to design waste and waste, store products and services, and rehabilitate environmental systems. Novo Nordisk's production of natural remedies, "yeast by far represents the largest amount of waste, and as a result they have a very good setup. residual biogas is used as a fertilizer in farmland as there are many nutrients left (Brown 2019) Some pharmaceutical companies look for green chemical solutions that use resources effectively, eliminate the use of toxic ingredients and chemical compounds, eliminate waste and hazardous products, and reduce consumption of energy throughout the product life cycle.

COVID-19 also brings focus back on pollution due to pharmaceuticals

India, however, has failed to control pollution in its medicinal areas such as Patancheru-Bollaram Industrial Estate in Telangana, Baddi Industrial Area in Himachal Pradesh, and SIPCOT Industrial Estate in Cuddalore, Tamil Nadu. This apart from the laws of Environment (Protection), 1986, applies. New Indian medical parks have been set up at these locations. In a recent meeting with NITI Aayog, the Department of Pharmaceuticals promised fast environmental clearances to the industry. Such immediate corrective measures can be harmful over time without strict enforcement. India needs to be very careful now.

The pandemic, however, has given the world an opportunity to rethink the pharmaceutical industry. Countries have realized that their over dependance on others can be a major problem. They are now trying to be independent (Varshney et al. 2020).

CONCLUSION

There is a lot of research going on in industry, research labs and educational institutions; with a minimal regulation and control on educational institutions. The number of patent cases reflects the amount of research conducted in the field of antimicrobials over the past decade. The increase in patents over the past three years has been matched by an increase in virus resistance and / or an increase in government funding. Uncontrolled research also leads to increased environmental threats. The government needs to come up with specific regulations and strict policies to monitor and regulate research activity and the use of all chemicals and reagents. Only then will we be able to find the balance between science and nature, which is the need of the hour.

Limitations and challenges

Indian law appears to be a complex set of rules, notices and requirements for approval. Pollution mitigation policies relies heavily on effective monitoring infrastructure and reliable data execution. Indian pollution monitoring agencies are plagued by a variety of challenges - from inadequate workforce, poorly trained workers to dilapidated infrastructure. It is hoped that a portion of the Rs 4,400 crore allocated to the National Clean Air Program will be invested in strengthening these administrative lacunas. Another important factor is to ensure strong implementation of standard control measures and enforcement measures, including closing down factories that are found to be noncompliant and penalizing companies that operate them. Without implementation and strict enforcement, the desirable rules will be the only smoke screen for implausible practices.

Table 1: Recent reports on drug-environment related activities.

Author	Activity/Action	Available at
T. Mohan 2020	The Union Ministry of Environment, Forests and Climate Change (MoEFCC), notified draft environmental standards for the bulk drug and pharmaceutical manufacturing industry.	https://science.thewire.in/environment/pharma-pollution-tuberculosis-antimicrobial-resistance-patancheru-bollaram-ngt/
News and Opinions 2020	Proposed Environment (Protection) Amendment Rules, 2019, which sets limits on residues of 121 antibiotics in the treated effluents discharged by drug production units	https://www.reactgroup.org/news-and-views/news-and-opinions/year-2020/antibiotic-pollution-india-scores-a-global-first-with-effluent-limits/
Natasha Gilbert 2020	After global leaders committed to tackling AMR, more than 100 drug companies and industry associations formed a group—the AMR Industry Alliance—in part to police manufacturing discharges	https://www.sciencemag.org/news/2020/01/industry-says-voluntary-plan-curb-antibiotic-pollution-working-critics-want-regulation
U Sudhakar Reddy 2020	BDMA objects to changes in environment protection rules	https://timesofindia.indiatimes.com/city/hyderabad/bdma-objects-to-changes-in-environment-protection-rules/articleshow/76703555.cms
Laxmi Yadav, 2020	Industry urges govt to simplify guidelines of EIA Notification to fast-track approvals for API production	http://www.pharmabiz.com/NewsDetails.aspx?aid=129471&sid=1

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