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ENVIRONMENTAL RISK ASSESMENT OF PHARMACEUTICALS: GLOBAL REGULATORY PERSPECTIVES

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INTRODUCTION

Medicines play an important role in the treatment and prevention of disease in humans and animals. During their manufacture and use, they may be released to the environment by a number of routes.[1-3] Even though the side effects on human and animal health have been widely documented, only recently have the potential environmental impacts of the manufacture and use of medicines been considered. Pharmaceuticals are introduced into the environment through various routes. Generally they enter the environment during manufacture or after use by both humans and animals. Potential pathways for human pharmaceuticals to enter the environment include[4-5]:

a) Release from pharmaceutical manufacturing facilities,

b) Disposal of unused pharmaceuticals by patients, hospitals, or distributors either to wastewater or to solid waste,

c) Patient excretion of pharmaceuticals and their metabolites to wastewater.

Human wastes are typically treated in sewage treatment plants (STP). During wastewater treatment, a drug may be degraded via hydrolysis, oxidation, or biodegradation, or the drug may adsorb to solids that are isolated in sludge. Pharmaceutical concentrations in STP effluents depend on the removal efficiency of the STP treatment processes. STP effluents are generally considered the primary source of human pharmaceuticals into the aquatic environment. The veterinary pharmaceuticals may pose more threat to ecosystems than human pharmaceuticals because of their characteristics of environmental release. When they are used in fish farms or excreted directly on land, veterinary medicines are released directly into the environment. They also indirectly enter into the environment when manure containing excreted pharmaceuticals is applied onto land. Since veterinary pharmaceuticals are typically non point source pollutants, it is more difficult to effectively manage their

contamination compared to human pharmaceutical contamination.[6] Pharmaceuticals have been detected in the environment since the late 1990s. Studies in Europe, Canada, Japan, India, China and the United States have reported the occurrence of pharmaceuticals in the aquatic environment. More than 100 pharmaceuticals from various therapeutic classes have been detected in sewage influent/effluent, surface water, groundwater, and even drinking water. In addition, it is worthwhile to note that there are many pharmaceutical substances that have never even been surveyed.[7]

An attempt has been made in the present work to study regulations regarding environmental risk assessment of pharmaceuticals in different countries and compare them to analyze the strengths and weakness of current regulations concerning environmental risk assessment of pharmaceuticals.

The United States

The US Food and Drug Administration (USFDA) is the primary federal agency responsible for the regulation of pharmaceuticals and personal care products in the United States. The agency's primary role is the assessment of applications for clinical investigation and the marketing of drugs and devices for human and animal use.[8] In FDA the act and penalty are very strictly implemented. National Environmental Policy Act of 1969 (NEPA). This law requires the US government to consider the potential environmental impact of .actions that the government takes. Approval of a marketing application for a human or animal drug is considered to be an action under the FDA specific NEPA regulations, and therefore the environmental impact of the marketed product must be assessed.[9-10] The FDA implemented a guidance document on the ERA of human pharmaceuticals in 1998. Specific product types are specified in the Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. (US FDA, 1998) and, in particular, some pharmaceuticals, which anticipate no expected impact on the environment, are categorically excluded from assessment and data requirements.[11] There are a number of categorical exclusions described in the US Code of Federal Regulations (21 CFR Part 25.31). These include situations in which the manufacturer can demonstrate that:

1. There is no increase in use of the active pharmaceutical moiety;
2. There is an increase in the use of the active moiety, but the release into the aquatic environment is less than 1 *ƒ* Êg/L (or EIC);

3. The drug is a naturally occurring substance, and there is no significant change in concentration or distribution of the compound in the environment.
4. The drug is in the investigational stage of clinical development. However, if extraordinary circumstances exist, then a categorical exclusion is not appropriate, and an environmental assessment should be submitted with the application. A brief overview of the FDA. Environmental assessment (EA) procedure for human drugs can be found elsewhere. Preparation of an environmental assessment ordinarily is required unless the proposed action qualifies for exclusion under 21 CFR 25.30 or 25.31. An EA would also be required if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21).

The European Union

Legally, all new European drug approvals need to satisfy the requirement of Directive 2004/27/EC (European Union, 2004) regarding environmental risk assessment.[12-13] The legislation concerning the requirements for the registration of human pharmaceuticals in Europe was driven by the European Commission (EC), based on the relevant Directive 93/39/EEC (European Union, 1993) and its changes up to 2001/83/EC and 2004/27/EC (European Union, 2001 and 2004). The 1993 Directive vaguely indicated the importance of an environmental risk assessment by stating that the dossier should contain if applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment (14-15). The initial impact of the directive merely required notification of potential environmental risks in broad terms. The latest versions of the directive (European Union, 2001 and 2004) broadened the impact by specifying its goals in several articles: Article 1, 28(1) assesses any risk of undesirable effects on the environment. Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment. In short, the initial phrasing of the directive required only a notification of any environmental risk with no further specification concerning what possible actions may be taken if such risks are identified. The recent version of the directive clearly names the environmental risk assessment (ERA) as a goal itself, followed by risk management actions on a case by case basis, if needed. The risk

management options are described vaguely as specific arrangements, which leave flexibility for the regulators and manufacturer in proposing such arrangements.

ERA procedures for pharmaceuticals in accordance with the EMEA regulatory guideline is a step wise, tiered procedure starting with rough estimates and progressing to more elaborate, refined methods if a potential risk cannot be excluded. The assessment may be terminated either when sufficient information is available, indicating that the product/compound is unlikely to represent an environmental risk, or when a risk has been identified and sufficiently characterized. A risk quotient (RQ) is usually calculated from a predicted (or measured) environmental concentration (PEC or MEC) and a predicted no effect concentration (PNEC). PEC can be calculated from a combination of estimates of the amount of consumption or sales, expected route of entry into the environment, and physico-chemical properties. In higher tiers, fate in the environment (such as biodegradability, bioconcentration, and adsorption to soil or sediment) is taken into account. A PNEC is obtained by dividing the lowest no observed effect concentration (NOEC) for the most sensitive species with an appropriate safety factor.[16]

Accordingly, the outcome of an ERA is dependent on amount used, environmental fate, and the ecotoxicity of the compound in question. More detailed requirements and procedures can be found in the guideline.

Canada

Health Canada requires the assessment of medicinal products regulated under the Food and Drug Act (F&DA) with respect to their potential effect on the environment.[17] If the substance is not included on the Domestic Substances List (DSL), it is considered new and is subjected to the New Substance Notification Regulations (NSNR) of the Canadian Environmental Protection Act 1999(CEPA).[18] The intention of these regulations is to implement a preventive approach to new substance management by requiring data on the substance before it can be manufactured or imported into Canada. Based on this data, Health Canada and Environment Canada conduct an assessment and determine: the risk of the substance to human health and the environment, whether controls may be warranted to mitigate risk, or whether additional information is required. The New Substances Notification process can ultimately result in the addition of a substance to the DSL. CEPA could be considered a safety net. In that it captures many of the substances not screened for environmental impacts under other federal acts or regulations.[19-20] CEPA endeavors,

however, to avoid legislative duplication by recognizing other federal acts and regulations that provide equivalent protection to the environment and human health. Environmental laws related to pharmaceuticals are good.

The original CEPA (CEPA, 1988) did not require notification of these new substances. In addition, at that time the Food and Drug Act (F&DA), the principal legislation regarding the safety and efficacy of foods and drugs in Canada, was considered to be exempt from CEPA. As a result, substances contained in commodities such as human drugs, biologics, veterinary drugs, cosmetics, novel foods, food additives, natural health products, and medical devices were not notifiable to the NSNR under CEPA 1988.[21]

India

In India the Department of Environment was established in India in 1980 to ensure a healthy environment for the country. This later became the Ministry of Environment and Forest in 1985. The constitutional provisions are backed by a number of laws – acts, rules and notifications. The EPA (Environment Protection Act), 1986 came into force soon after the Bhopal Gas Tragedy and is considered an umbrella legislation as it fills many gaps in the existing laws. Thereafter a large number of laws come into existence as the problems began arising, for example, Handling and Management of Hazardous Waste Rules in 1989. In India many of the developmental projects till as recently as the 1980s were implemented with very little or no environmental concerns. The environmental issues began receiving attention when a national committee on environmental planning and coordination was set up under the 4th five year plan (1969- 1978). Till 1980, the subjects of environment and forests were the concern of the Dept of Science and Technology and Ministry of Agriculture respectively. Later, the issues were formally attended by the Department of Environment which was established in 1980. This was then upgraded to the Ministry of Environment & Forest in 1985. In 1980, clearance of large projects from the environmental angle became an administrative requirement to the extent that the planning commission and the central investment board sought proof of such clearance before according financial sanction.[22]

Five year later, the Dept of Environment and Forests, Government of India, issued guidelines for environmental assessment of river valley projects. These guidelines require various studies such as impacts on forests and wild life in the submergence zone, water logging potential, upstream and downstream aquatic ecosystems and fisheries, water related diseases. Currently there are no guidelines or provision for ERA of pharmaceutical in India.[23]

However, an environmental cell was established in 2008 by Department of Pharmaceuticals; Ministry of Chemicals & Fertilizers. The cell was established with an objective of interacting with ministry of environment and forest (MOEF) and other related departments/institutions on all environmental issue pertaining to pharmaceutical sector. The environment cell will also collect knowledge and compile data on the latest technologies available for effluent treatment and disaster management and disseminate information among the pharmaceuticals industry. Cell will try and build partnerships with the Ministry of Environment & Forests, Government of India and the Central and State Pollution Control Boards to facilitate the process of environmental compliance for the sector.

In 2009, Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India, Federation of Indian Chambers of Commerce and Industry (FICCI) and National Institute of Pharmaceutical Education and Research (NIPER) had organized a Seminar on "Environmental Issues Pertaining to Pharmaceutical Industries" in New Delhi. The objective of organizing the Seminar was to identify the environmental issues that are being faced by the bulk drug industry in particular and pharmaceutical industry in general and to identify areas where the newly established Environment Cell under the Department can facilitate the process of environmental compliance for such industries to ensure environmental sustainability.

The seminar concluded with following recommendations:

a) Mechanisms need to be created for greater dissemination of information among stakeholders
b) Mass Spectroscopy (MS) and Liquid Chromatography (LC) are direct tests which can determine the presence of APIs in a medium. It is recommended that these tests should be included as part of the legislation. Centers can be established nationwide, such that small scale industries can access these services.
c) Larger pharmaceutical companies, who are able to implement "zero discharge" norms should be awarded some relaxation on product volume to enhance and facilitate/motivate industry.
d) Green processing and green engineering should be encouraged
e) Along with the issue of tackling effluent discharge from industries, an important concern which also needs to be addressed is that of air pollution and odour from the industrial units.

f) Funds should be available for implementation of cleaner technologies
g) Availability of funds for designing of cleaner manufacturing facilities and research and development
h) The current legislation does not prescribe separate rules for measurement of antibiotics. Inclusion would help in their detection
i) Pollution Control Boards can help in educating and creating awareness among industry stakeholders
j) Quality checks should be done during the process of manufacturing and not only at the point when the finished product is produced
k) Destruction of critical/high potent API effluent at the point of generation should be practiced and should also be evaluated quantitatively. This can be done by installing state-of-the-art "Kill Tank", which can be attached to the manufacturing plant
l) Industry needs to handle its environmental issues without the interference of Pollution Control Boards
m) Separate incinerators should be established for incinerating chemical and biological waste
n) Waste generated by one company can act as a resource for another industry. This concept may be adopted by the industry as it will facilitate in achieving the zero discharge norm.

Japan and China

China has signed Basal Convention which is concerned with the trans-boundary movements of hazardous waste which is also applicable to hazardous health care waste. Countries that signed this convention accepted the principle that the only legitimate trans-boundary shipments of hazardous waste and exports from countries without facilities, or expertise to dispose safely of certain wastes to countries which have both – facilities and expertise. Exported waste should be labeled according to the United Nations recommended standards. Pharmaceutical manufacturers in China also need to comply with the relevant laws and regulations passed by the State and local government environmental protection departments.[24] The major relevant laws are the Environmental Protection Law of the PRC the Law of the PRC on Prevention of Water Pollution Law of the PRC, the Implementation Rules of the Law of the PRC on Prevention of Water Pollution, the Law of the PRC on Prevention of Solid Waste Pollution, and the Law of the PRC on Prevention of Air Pollution. Enterprises discharging any pollutants in their daily operations and manufacture shall observe the national discharge standards which are regulated by the Ministry of Environmental Protection of the PRC, which has established various discharge standards, as amended and

revised from time to time, with regards to discharge of water pollutants, solid pollutants, gas exhaust, noises and other pollutants.

At present, there is no legal requirement for an environmental risk assessment of human pharmaceuticals in Japan. However, the Ministry of Health, Labour and Welfare (MHLW) is investigating the fate and effects of pharmaceuticals in the environment.[25] Japanese legislation related to the administration of chemicals is of two types, one group handling all chemicals, and another group dealing with specific chemicals. Specifically, Japanese laws related to the administration of chemicals include the following:

a) The Chemicals Testing Law
b) Pollutant Release and Transfer Register (PRTR) Law
c) The Law Concerning the Regulation of the Testing and Manufacturing of Chemicals (the Chemicals Testing Law)
d) The Law Concerning the Securing the Enforcement of the Collection and Destruction of chlorofluorocarbons (CFCs) (the CFC Collection & Destruction Law)
e) The Law Concerning the Protection of the Ozone Layer by Regulation of Designated Substances (the Ozone Protection Law).

The Chemicals Testing Law strives to establish a system where a party seeks to manufacture or import new chemicals to test the characteristics of the chemicals in advance, in order to prevent environmental pollution by chemicals that are difficulties decomposing in the environment and that damage health.[26] To sum up the regulatory perspectives regarding the environmental risk assessment of pharmaceuticals in different countries reveals that there is an urgent requirement of including these factors as a part of new drug registration. Some countries have already adopted this and other countries also need to include these regulations to ensure that our environment is free from adverse effects of pharmaceuticals.

CONCLUSION

Present study has revealed wide variation in environmental risk assessment of pharmaceuticals in different countries. In countries such as USA, EU, CANADA, there are strong guidelines for environmental risk assessment of pharmaceuticals. However, in countries such as India, China and Japan, there are no such guidelines available and multiple laws are used to manage pharmaceutical pollution. Rapidly changing global scenario necessitates urgent need for complete harmonization in the present day regulation regarding environmental risk assessment of pharmaceuticals. Green processing and green engineering

should be encouraged. Waste generated by one company can act as a resource for another industry. This concept may be adopted by the industry as it will facilitate in achieving the zero discharge norm. Pharmaceutical regulators, manufacturers, environmental ministry/pollution control boards and society needs to come together and show a great desire and determination to protect our environment from the harmful effects of pharmaceuticals and ensure a clean environment for our generations to come.

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