# Pharmacovigilance

SECTION EDITOR

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## Editorial

The PV section in this issue opens the door to a very interesting topic: ecopharmacovigilance. This article is the result of a collaboration among volunteers of EMWA's Pharmacovigilance Special Interest Group (PV SIG) and the Ecopharmacovigilance SIG at the International Society of Pharmacovigilance (ISoP). The authors have realised that there is an urgent need to measure the impact and understand the current picture of the problem of unintended environmental exposure to pharmaceuticals. Awareness must be raised between the different stakeholders through education and training.

While the problem of incorrect disposal of pharmaceutical waste is a well-known and relevant issue from a perspective of environmental risk and sustainability, I think that only very few among us have ever regarded it as a potential area for synergy and risk minimisation from a pharmacovigilance perspective. This article will open our mind to new perspectives!
I wish everyone happy reading!

**Tiziana von Bruchhausen**
**Chair of the PV SIG**

# Ecopharmacovigilance: A review of cause, impact, and remedies

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## Introduction

Pharmaceuticals contaminating the environment is a well-known, multidimensional problem. Biologically active pharmaceuticals and their metabolites can have off-target effects when they enter the environment. The UN Environment Program has identified environmentally persistent pharmaceutical products (EPPPs) as a serious problem requiring urgent policy remedies.[1] Recognising these grave concerns, some regions,[2] companies,[3,4] and countries such as Bhutan, Canada, Colombia, Ghana, India, Israel, Liberia, Lithuania, Sri Lanka, the European Union, and the United States, among others, have enacted measures to reduce the environmental impact of pharmaceuticals.[5–12] An example is the European Union where during drug development, manufacturers are mandated to conduct environmental impact testing of human (and veterinary) drugs (both for GMOs and non-GMOs), and include clear wording in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) on proper drug disposal.[13,14] However, other countries have inadequate or non-existent guidelines and regulations.

## Sources of pharmaceutical waste

Pharmaceutical waste comprises a broad set of waste products from using or disposing of medicine and medicinal products. The WHO defines pharmaceutical waste as "expired, unused, spilled and contaminated pharmaceutical products, prescribed and proprietary drugs, vaccines and sera that are no longer required and due to their chemical or biological nature, need to be disposed of carefully".[15] According to the National Health Service, of the United Kingdom, pharmaceutical waste in the healthcare setting can arise from the following:[16,17]

1. **Non-compliance:** Patients do not take medicines as prescribed. For example, taking at irregular intervals or in incorrect doses leads to unused drugs which are eventually discarded.
2. **Intentional non-adherence:** Patients stop taking medication due to adverse events or personal beliefs.
3. **Unintentional non-adherence:** Patient forgets and stops taking medicines or fails to take them at correct time intervals due to forgetfulness.
4. **Non-preventable waste:** Patients die, and medications remain unused, or a change in treatment means current dispensed medicines are no longer required.
5. **Preventable waste:** Patient stockpiles medicines "just in case." All items from repeat prescriptions are dispensed even if the patient no longer takes medications.

Additionally, sources of pharmaceutical waste include improperly disposed medications, effluents from pharmaceutical manufacturing plants, excretion of metabolites by patients, and the irrational use of medications in agriculture, among others.[18] Manufacturers sometimes include information on safe disposal of expired medications in the SmPC and PIL, but consumers do not always follow such guidelines.

## The burden of improper disposal of pharmaceutical waste

Over time, little attention has been paid to the environmental impact of pharmaceuticals. Until recently, very few studies have estimated the burden of pharmaceutical products on the environment; these studies are limited to a few countries. The methods used were often non-standardised, making comparisons difficult. Drug usage in both humans and animals is ever-increasing. One study projects that the global consumption of veterinary antimicrobials will be more than 100,000 tons by 2030.[19] Earlier reviews, mostly from high-income countries, demonstrated the presence of pharmaceuticals in water bodies.[18] However, one of the most extensive studies estimating the presence of medications in 1052 rivers across 104 countries showed that the most contaminated rivers were in the low-middle-income countries of sub-Saharan Africa, South Asia, and South America.[20] The need for the safe disposal of medicines is an issue today, but awareness among healthcare

professionals and consumers is low.

There are already some examples of regulations in this field such as those from the EMA, and the US FDA.[13,21] For example, in Europe, throughout drug development, manufacturers are mandated to conduct environmental impact testing of human (and veterinary) drugs (both for GMOs and non-GMOs) and include clear wording in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) on proper drug disposal[13] Provision of clear disposal guidelines by manufacturers in the SmPC and PIL[22] and strict adherence by end users can help to decrease the environmental load of medicines. Some authors argue that the burden of responsible disposal should be shared between government, patients, and pharmaceutical companies.[23] Pharmacovigilance professionals can be at the forefront and create a movement, especially since they are in a unique position to educate all relevant stakeholders about safe medicine use and its disposal. Proper patient counselling on safe medication disposal can significantly impact this critical public health challenge. A practical approach would be to prioritise this issue in the training curricula of all healthcare workers. Establishing cost-effective and acceptable government-run collection and disposal systems constitute a long-term solution. Manufacturers and regulatory authorities need to work together to develop a framework for environmental risk assessment of medications and establish and evaluate risk minimisation activities.[24] This multidisciplinary approach requires all the stakeholders – governments, non-governmental organisations, physicians, pharmacists, patients and the public, to work synergistically to reduce the burden of pharmaceuticals on the environment.

## How can we integrate ecopharmacovigilance into existing pharmacovigilance systems?

Pharmacovigilance comprises a whole range of routine activities and an expanding scope of unique activities beyond the regular reporting of Adverse Drug Reactions. As described in the EMA Good Pharmacovigilance Practices guidelines, additional pharmacovigilance activities have been recommended to identify delayed safety concerns.[25] Some regulatory agencies such as the EMA[13] require the manufacturer to conduct a risk assessment that estimates the concentrations that will be found in the environment in order to gain market approval. Low concentrations (defined by USFDA as less than one part per billion) are assumed to pose only acceptable risks (but still a risk!).[26] We now know that pharmaceuticals' environmental impacts are often so slow and inconspicuous that they go unnoticed until it is very late. Ecopharmacovigilance could very well be proposed as an additional risk minimisation activity. Some authors have proposed targeted implementation focusing on the monitoring of the occurrence of high-priority pharmaceuticals in environmental samples, the management of primary emission sources, legislation and research on high-priority pharmaceutical pollutants, as well as the targeted educational strategies for specific vital populations.[27] These proposals, in turn, can influence the health of these animals and eventually humans.


The ongoing success of pharmacovigilance programmes in various countries is a good reason to suggest that pharmacovigilance is best positioned to take on extra activities, dealing specifically with the effects pertaining to the environment. Ecopharmacovigilance can be easily incorporated within the routine activities of existing pharmacovigilance programmes with close collaborations with manufacturers and responsible regulatory agencies.[28] Through urgent passing and implementation of strict regulations, there remains the hope of reversing or preventing further impact on the environment and food chain. Education and training in ecopharmacovigilance and environmentally conscious prescribing are essential components identified by some researchers that could significantly impact how medicines are used and disposed of.[29]

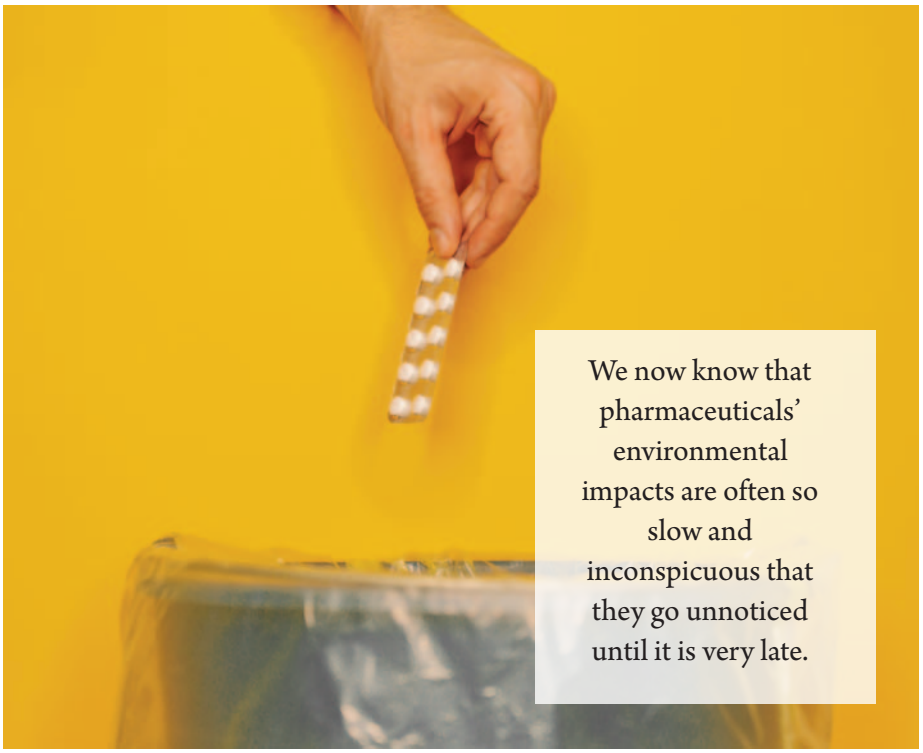
Taking cues from operational history of pharmacovigilance programmes, successful strategies such as spontaneous reporting, intensive monitoring and database studies, have been proposed as starting points for ecopharmacovigilance.[30] These activities can be implemented for continued environmental risk assessment of products approved by the pharmaceutical regulator.

## Conclusion

The presence of pharmaceuticals and their active metabolites in the environment is a cause for great concern. A concerted multidisciplinary approach is needed to tackle this menace. Countries which have non-existent or inadequate environmental regulations can learn from success stories like the EMA and USFDA. The current scope of pharmacovigilance activities must be extended to include aspects of ecopharmacovigilance, and "pharmacovigilantes" can easily contribute their skills toward this cause. Lessons drawn from the successes and challenges of ecopharmacovigilance will be used to improve the discipline further.

## Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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