

Ins and outs of environmental risk assessments (ERAs) of medicinal products for human use

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Abstract

An environmental risk assessment (ERA) is the process of evaluating the effects of drugs for human use on the environment. ERAs must accompany all new drug market authorisations in Europe. In this article, we discuss the current guidelines on ERAs for drugs without genetically modified organisms for human use. We also discuss the role of medical writers/communicators and aspects of the guideline that may be improved upon.

Pharmaceuticals are a vital component of the medical profession's arsenal to prevent and cure illness and maintain health. Availability of and access to effective pharmaceuticals benefit society in terms of improved quality of life, productivity and longevity.¹ However, simultaneously, pharmaceuticals are a threat to the planet's health and since the 1990s, awareness of the environmental risks of pharmaceuticals to water (ground, surface, sewage), soil, air, and biota has grown.²

Indiscriminate use of antibiotics in humans, pharmaceutical manufacturing facilities, and agriculture has resulted in antibiotic run-off into the environment that, together with the natural bacterial communities and the discharged resistant bacteria, create "superbugs".^{3,4} Such events can see the emergence of pathogens with

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antibiotic resistance genes (ARGs), which are a bigger challenge to treat.⁴ Another concern is the emergence of endocrine disrupting chemicals (EDCs). They are non-natural chemicals that can disrupt hormonal action when ingested by mimicking the hormones, affecting the hormonal pathway, altering the receptors, or acting as hormone antagonists. Some of the modern drug delivery systems (intravenous, oral, and transcutaneous routes) contain nanoparticles and microplastics that are probable EDCs and thus, can disrupt hormonal functions in the human body. Moreover, EDCs can also be passed from the mother to the foetus,⁵ are ubiquitous, and can make their way to water bodies.

Minimising the impact of pharmaceuticals on the environment is part of Good Clinical Practice (GCP) and is stated in the 11th principle of the Declaration of Helsinki.⁶ Furthermore, conducting environment risk assessments (ERAs) for the risks associated with the use of medicinal products is part of EMA's regulatory submission for market authorisation application (MAA). It should be noted that the risks associated with the synthesis or manufacture of medical products is outside the scope of ERAs. The legal basis of ERAs for human medical products (HMPs) can be found in Article 8(3) of Directive 2001/83/EC and Directive 2001/18/EC.⁷ ERAs are submitted as part of Module 1.6 of the electronic common technical document (eCTD).⁷ The two main guidelines for ERAs of medical products for human use are:

- the EMEA/CHMP/SWP/4447/00 Rev. 1 (2018) for medicinal products for human use in general;⁷ and
- the EMEA/CHMP/BWP/473191/2006 – Corr (2006) for medicinal products containing, or consisting of, genetically modified organisms (GMOs).⁸

In this article, we provide an overview of the guidelines on ERA for drugs for human use without genetically modified organisms (GMOs). We also discuss the role of medical writers and communicators in the preparation of ERAs and aspects of the guidelines that may be improved upon.

ME/CHMP/SWP/4447/00/Corr2 (2006) for human medicinal products

ERAs for HMPs follow a two-phase, stepwise assessment procedure (Figure 1), similar to that for veterinary medicinal products.⁹ The results at the end of Phase I determine whether the Phase II Assessment is required. However, certain substances such as EDCs and antiparasitics undergo Phase II Assessment regardless of their Phase I outcome. It is also possible that an ERA consists solely of a justification for not submitting ERA studies.⁷

The active pharmaceutical ingredient (API) is usually the parent compound. ERAs are based on a "total residue approach", which has two assumptions: the body does not metabolise the API and excretes it as the parent compound, and metabolites have similar or lower toxicity than that of the parent compound.⁷

Phase I: Environmental exposure screening

The exposure estimated at this phase is based only on the API and not on the route of administration, pharmaceutical form, metabolism, and excretion.

In Phase I, the following types of studies may be conducted:

- Risk assessments to determine the possibility of an organism in the environment becoming exposed to the API and ecotoxicity occurring;
- Persistent, bioaccumulative, and toxic (PBT) assessments, which evaluate the degree to which APIs degrade in the environment (persistent), accumulate in organisms (bioaccumulative),

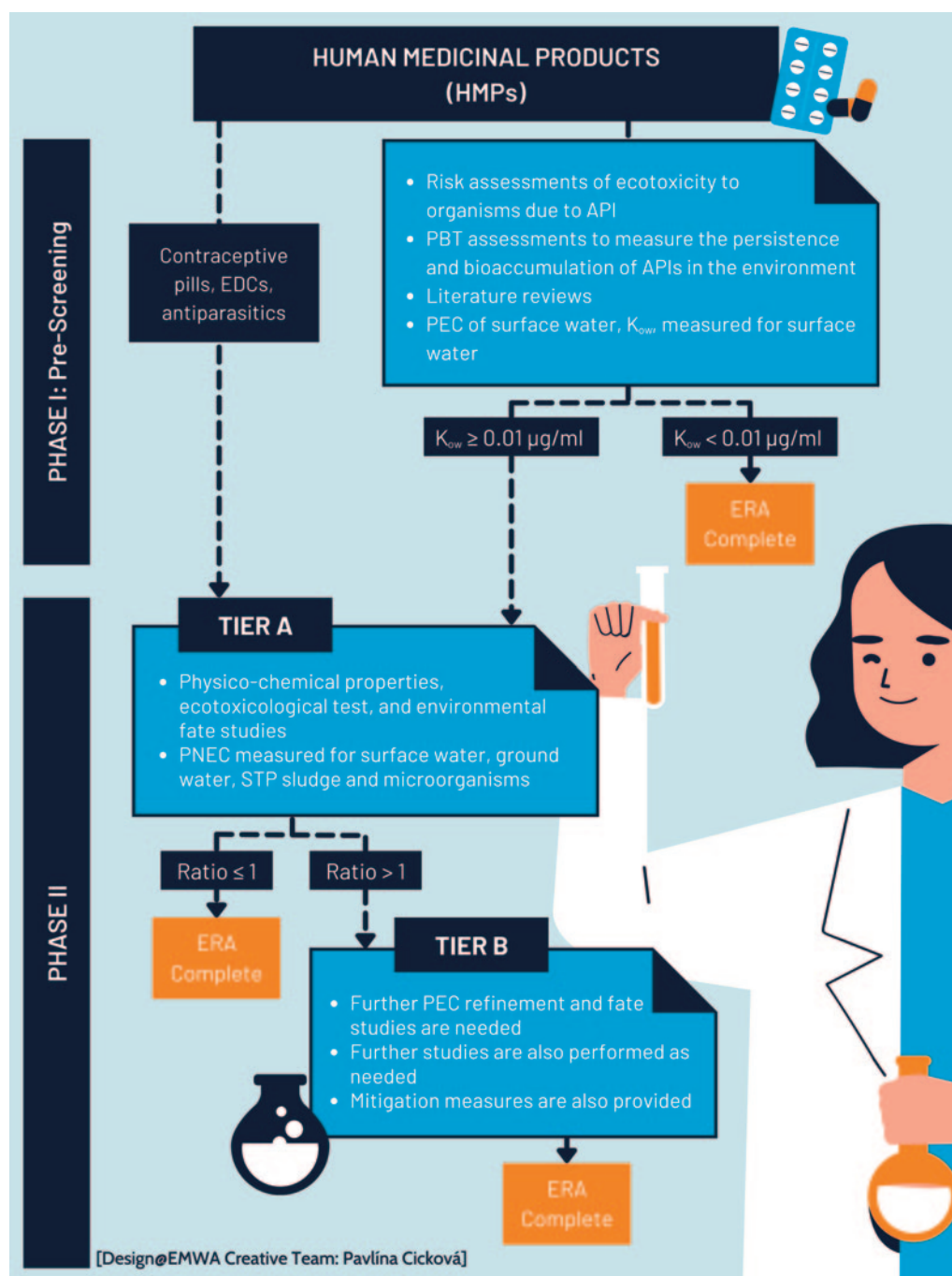


Figure 1. The environmental risk assessment (ERA) process outlined by EMA.

Abbreviations: API, active pharmaceutical ingredients; PBT, persistent, bioaccumulative, and toxic; PEC, predicted environmental concentration; PNEC, predicted no effect concentration; STP, sewage treatment plant; EDCs, endocrine disrupting chemicals.

and are toxic. PBT assessments address the intrinsic properties of APIs, which make long-term environmental risks unpredictable

- Complete literature reviews.

The next step is the calculation of the predicted environmental concentration (PEC) of surface water, measured as K_{ow} . If the value is less than $0.01 \mu\text{g/l}$, then further tests are not conducted and the drug substance is considered to not pose any danger to the environment and the ERA is complete.⁷ However, as mentioned earlier, this does not apply to any APIs such as EDCs that disrupt reproduction in vertebrates.⁴ When the

value of K_{ow} is equal to or above $0.01 \mu\text{g/l}$, then the drug substance enters Phase II.⁷

Phase II: Environmental fate and effects analysis

Phase II consists of two tiers, A and B. In Phase II, the following studies of the APIs may be conducted:

- Physico-chemical properties
- Environmental fate
- Ecotoxicological effects
- Mechanism of action

The studies address environmental risk for soil, water (ground, surface), functioning of sewage treatment plants, sediment, and secondary poisoning of predators. In Tier A of Phase II studies, predicted no effect concentration (PNEC) is calculated for surface water, ground water, and microorganisms. If the ratio is less than one, the API is considered safe, and no more testing is required. If the ratio is above one (above 0.1 for microorganisms), then Tier B tests for fate and effects assessment are required (see Figure 1). ERA guidelines state that if animal studies are conducted, such studies should

implement the 3R principles of animal welfare (replacement, reduction, refinement) in accordance with Directive 2010/63/EU for studies to be Good Laboratory Practices (GLP)-compliant and follow test guidelines issued by the Organization for Economic Co-operation and Development (OECD), European Commission, or comparable guidelines.⁷

How are findings from ERAs used?

If findings of an ERA indicate that the possibility of environmental risks cannot be excluded, then the applicant proposes appropriate risk mitigation strategies to minimise release of the medical product into the environment. Currently, the key mitigating strategy is to provide clear instructions for proper disposal of the medicinal product, e.g. returning used patches, medicine delivery devices, and unused medicines to the pharmacy or recycling centres with designated collection boxes. Other strategies include presenting information about potential environmental risks and proper storage, and use of the medicinal product on package labelling and inserts (information for use). With regard to aquatic toxicology studies and fate studies, sharing information on analytical verification of APIs on a given applicant's website or in a general database is "encouraged". This is so that those in water management are able to monitor substances of concern.¹⁵ However, the quantity and quality of data sharing are currently debatable.^{10,11}

ERA structure and the role of medical writers in writing ERAs

ERAs are part of MAA of HMPs and they have a well-defined structure. The introductory section requires a clear identification of the active ingredient, including company name/code, International Union of Pure and Applied Chemistry (IUPAC) name, Chemical Abstract Service (CAS) number, empirical formula, structural formula, Simplified Molecular Input Line Entry System (SMILES) code, and molecular weight.⁷

If relevant, a rationale for the absence of environmental studies is provided. Otherwise, the studies from Phase I and/or Phase II are summarised as texts and tables, as required. The full study reports and references are listed in the annex of the ERA. Finally, the document must carry a dated signature of the author, information



on the author's education, training, and professional experience, and a statement of the author's relationship with the applicant.⁷

A medical/scientific writer working for pharmaceutical companies can write ERAs in collaboration with the scientists/toxicologists involved, who can oversee and review the documents. This is because medical writers have a strong understanding of the science involved and experience in translating documents into a structured, well-written study report. Such teamwork can produce a well-rounded document for submission to the EMA. Furthermore, medical communicators may communicate the findings from ERAs to the public in plain language, which exemplifies their vital role in society.

Some shortcomings in the current ERA regulation

There are a few shortcomings in the current ERAs for HMPs.

The first is related to harmonisation. Currently, module 1.6 of the CTD is a nation-specific chapter. As such, ERA requirements are not necessarily harmonised across the EU as are other components of a regulatory submission.¹² In addition, while improvements have been made, discrepancies with other environmental assessment guidelines still exist. For example, the current ERA guidelines are not harmonised with the Classification, Labelling and Packaging (CLP) Regulation, and there are differences between the PNEC and Environment Quality Standard (EQS) approaches.¹³

Second, the ERAs bring the onus of the user-created risks to the environment and ecosystem on the manufacturers to ensure that manu-

facturers evaluate the benefit-risks of HMPs and offer mitigation measures. However, these assessments do not look at the manufacturing processes and the subsequent release of API and other chemicals into the environment. Changes in ERA requirements such as including an assessment of risk during the manufacturing process would increase this document's relevance.²

Third, Wess et al. identified that current ERA guidelines do not include antibiotic testing requirements to evaluate their impact on critical microscopic, planktonic algae called diatoms.¹² As diatoms generate about 20% of the earth's oxygen annually,¹⁴ they should be part of environmental assessments as well.

Last, the public cannot access the complete ERAs created by manufacturers of HMPs and other official assessment reports based on them. Currently, the law only requires the publication of public assessment reports (PARs), which do not necessarily contain information from the ERAs.¹⁰ Also, manufacturers who are the authorisation holders of HMPs may exercise the right to refuse disclosing contents of ERA by citing that the ERA is commercially/industrial confidential information (CCI).¹⁰

However, Oelkers¹⁰ recently published arguments that under environmental information law, the release of pharmaceuticals into the environment constitutes an "emission into the environment". As such, there is a legal basis for full public disclosure of ERAs and their official assessment reports. Sharing data on APIs through publicly accessible databases is proposed as a resource-saving solution.¹⁰ This is a precondition for being able to detect emerging environmental trends and risks early and to prevent resource waste from unnecessary repetition of (animal) studies and loss of knowledge. The Swedish Pharmaceuticals and Environment database is an example of such an effort.¹¹

Conclusions

While pharmaceuticals provide society with health benefits, they are also a threat to the planet's health. ERAs aim to identify the environmental risks and ways to mitigate them at the user level. Medical writers and communicators are well-suited to collaborate with toxicologists and communicate the findings of ERAs to the public. Coordinated efforts by governments, regulators, and pharmaceutical

companies to promote and facilitate data sharing from ERAs are critical for planetary health.

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The opinions expressed in this article are the authors' own and not necessarily shared by their employers, clients, or EMWA.

Disclosures and conflicts of interest

Kimi Uegaki provides freelance medical writing and editing services to clients in academia and the biomedical/health care industry. Archana Nagarajan declares no conflict of interest.

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