Environmental Risk Assessment for Pharmaceutical Drugs

Understanding the Evaluation and Implications of Findings to the Regulatory Review of Human Medicines in the Environment

Introduction

Pharmaceutical drugs are intended for the treatment of human disease; therefore, the risk of their environmental exposure in clinical use needs to be evaluated. Environmental risk assessment (ERA) is part of the requirements when applying for marketing approval in many geographic regions throughout the world.

Many prescribed drugs taken by patients, irrespective of their administration route (oral, intravenous, subcutaneous, etc.), are excreted in urine and feces, either unchanged or as a metabolite of the original drug. Thus, drugs and/or their metabolites enter the sewage system and via the sewage treatment plant, enter the soil, surface water and groundwater (see Figure 1). A drug can also enter the environment in the air through exhalation. The impact on micro-organisms, plants and animals (invertebrates and vertebrates) living in these environmental compartments is a cause for concern.

Guidelines, therefore, have been produced to assess the impact on the environment. In the case of many therapeutics, such as biopharmaceuticals (containing, amino acids, peptides, proteins, nucleic acids, carbohydrates and lipids) as active pharmaceutical ingredients, an ERA is still conducted. This assessment will usually result in a justification for not performing any ERA testing. Due to the nature of these products, they are unlikely to result in a significant risk to the environment unless they have been extensively chemically modified. The same applies to many vaccines and advanced therapy medicinal products (ATMPs), although their own risk of environmental exposure risk is assessed in other guidance and legislation not covered in this white paper.

> Note: drugs can also enter the environment through the manufacturing process; however, this route is subject to different guidelines and will not be considered further in this paper.

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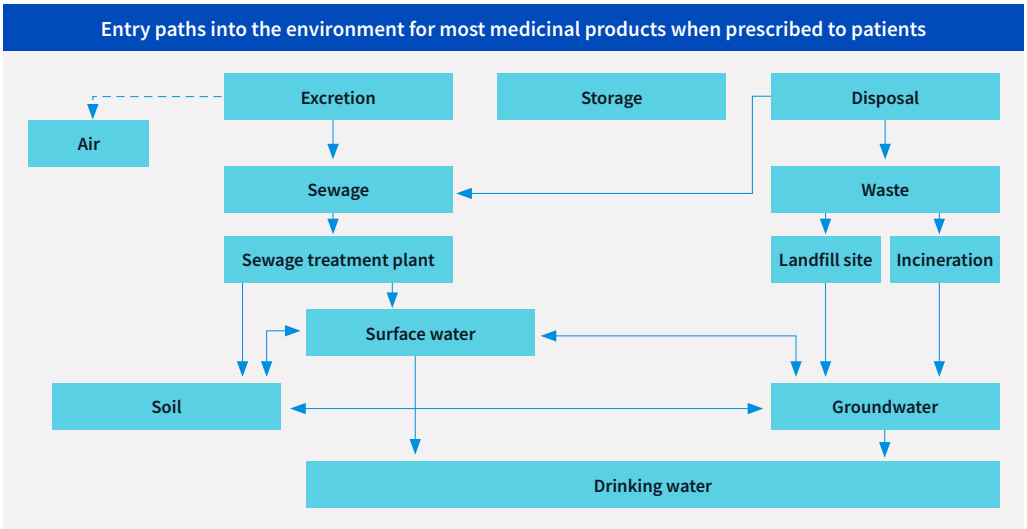
Figure 1: Route of Entry of the Pharmaceutical Drug into the Environment (Adapted from EMA guideline, 2006)



ERA Guidelines: Why Do Pharmaceutical Developers Need Assessment Programs?

An ERA is mandatory for pharmaceutical drug development according to international guidelines. This paper will focus primarily on the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) guidelines.

EU

All new drugs and generic compounds need to undergo an ERA according to the EMA's Guideline on the environmental risk assessment of medicinal products for human use; this was introduced in 2006,[1] with a follow-up Q&A document published in 2016.[2] The ERA is required for all new marketing authorization applications, as well as most variations and extension applications with increased environmental exposure. New guidelines are expected following a consultation period for comments that expired in 2019 with full updated guidelines expected in 2023.

Drugs intended for the EU market tend to require more robust ERA packages; therefore, these will be the primary focus of this paper; however, the studies conducted according to EU regulations have also been used for submissions in the U.S.

U.S.

A different and much simpler process operates in the U.S. Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications were introduced in 1998;[3] further guidelines for specific drug categories – Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic or Thyroid Activity: Guidance for Industry – were introduced in 2016.[4]

According to these U.S. guidelines, a simple calculation is required initially, based on the predicted annual production of the drug in the five years following marketing authorization (this is considered later in the process by the EMA). If the production is less than ~46,000 kg/year (equivalent to a concentration at the point of entry into the aquatic environment of less than 1 part per billion) is predicted for the U.S. market, an ERA is not needed and a categorical exclusion can be requested. A short report can then be submitted to the authorities.

If the production is greater than ~46,000 kg/year as predicted, a tiered approach to fate and effects testing must be followed. Often studies that have already been conducted for the EU authorities can be used for the U.S. FDA, if such studies are required. Drugs with estrogenic, androgenic or thyroid properties must be assessed following the 2016 guidelines.

Phased Approach to ERA in the EU

Considerations

The general principle of the regulations is to evaluate, in a phased approach, whether a drug and its metabolites, once released into the environment, have adverse effects due to persistence, bioaccumulation or toxicity to critical species in various ecosystems. The ERA is part of the development program for a drug and is usually conducted during clinical development Phase II/III (see Figure 2). This is important because completion of the overall ERA package can take up to two years, and ideally, it should be ready in time for marketing authorization. However, if started too early, before the drug has been assessed in patients, there may be unnecessary costs as the ERA might be performed for a drug that does not reach the market for clinical efficacy or safety reasons.

When initially considering the use of an ERA service provider, a pharmaceutical developer will be advised to present the details of its drug as fully as possible, including the name, structure, maximum expected daily dose, epidemiology and the patient population. For generic compounds, the pharmaceutical developer may only be required to demonstrate that there is not a significant increase in the environmental exposure to their compound.

With this information, the ERA service provider will be able to assess as to whether a waiver could be obtained for some or all of the tests. An ERA should then be provided with a justification for not submitting studies.

Similarly, some relevant test results may already be in the public domain, and it may be possible to write the ERA report using this information, if the quality of the work is acceptable.

In some cases, the ERA service provider can submit a position document to the regulatory authorities on behalf of the pharmaceutical company, which may be successful in waiving further tests

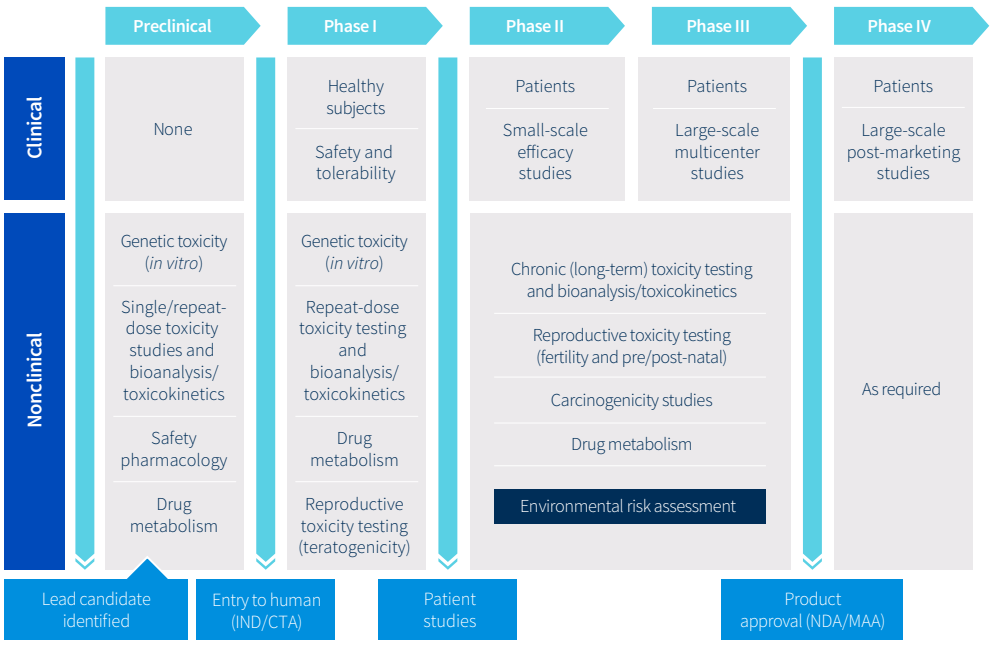


Figure 2: The Development Program for a Drug, Showing Timing of the ERA

The regulatory affairs group at Labcorp has obtained many waivers from the regulatory authorities: between 2009 and 2021, much of the required testing for over 20 products were waived. Compared with the cost of a full ERA testing program, this led to savings of more than $13 million (excluding radiosynthesis) for our sponsors. (see Table 1).

Table 1: Waivers Won by Labcorp: 2009–2020

Year of Waiver	Number of Waivers	Example of Studies Waivered	Amount Saved ($, K)
2009	2	Aquatic toxicity and bioaccumulation	300
2010	3	Aquatic toxicity and environmental fate	400
2012	3	Tier A and B; two fish full lifecycle studies	2,250
2013	4	Tier A and B; three fish full lifecycle studies	3,400
2014	2	Tier A	350
2015	3	Tier A and a full fish lifecycle study	1,800
2016	3	Tier A and B; two fish full lifecycle studies	3,000
2017	2	Tier A and a full fish lifecycle study	1,700
2019	2	Tier A	800
2020	1	Aquatic toxicity and environmental fate	400
		Total Saving	**14,400**

Phase I: Estimation of Exposure

In line with EMA guidelines, ERAs are conducted following a phased approach (see Table 2). An in-depth understanding of the physicochemical properties of the drug, persistence (P), bioaccumulation (B) and toxicity (T) issues, and epidemiologic data is essential. The pharmaceutical company may already have data that can be used; otherwise, tests will need to be performed.

The first step in Phase I is screening for PBT issues; this is necessary if the value for the octanol/water partition coefficient (log Pow) at around pH 7 is >4.5 at any pH in the range of 5-9.

The next step in Phase I is the calculation of the predicted environmental concentration in surface water (PECsw). Default values are used but can be refined using reliable epidemiological data. Phase II is triggered if the PECsw equals or exceeds 0.01 µg/L (equivalent to a maximum daily dose of the drug of 2 mg). If Orphan status is granted, based on reliable epidemiologic data, then the PECsw may become lower than the trigger value at higher drug doses.

Table 2: The Phased Approach to ERA: Tests Required at Each Phase

Stage of ERA	Objective	Test/Data Required
Phase I	Estimation of exposure	• Octanol/water partition coefficient for screening for PBT • Predicted PECsw: PECsw ≥ 0.01 µg/L → Phase IIA
Phase II Tier A*	Initial prediction of risk	**Physicochemical, fate and effects studies:** • Adsorption/desorption (batch equilibrium method) • Ready biodegradability • Aerobic transformation in aquatic sediment systems • Algae, growth inhibition • Daphnia, reproduction • Fish, early life-stage toxicity • Activated sludge, respiration inhibition • Water solubility and dissociation constant
Phase II Tier B*	Substance and compartment-specific refinement and risk assessment	**Extended data set on emission, fate and effects:** • Sediment dwelling organism • Fish bioaccumulation • Aerobic transformation in soil • Soil micro-organisms: nitrogen transformation • Terrestrial plants, growth • Earthworm, acute toxicity** • Collembola, reproduction
Additional	Assessment of potential endocrine disruptor	After an assessment of relevant toxicology results and modeling, it is advisable to discuss with regulators which studies might be required. **Such studies include:** • Fish short-term screening for estrogen/androgen and aromatase activity • Fish sexual development • Fish full lifecycle • Medaka (Japanese rice fish) extended reproduction

**Tier A and B studies may be different when the updated Guideline is published.*
***The earthworm acute toxicity may be replaced by a reproductive study.*

Phase II Tier A

Phase II is divided into Tier A and Tier B, with Tier B triggered by some Tier A studies.

Tier A includes the following studies:

Environmental Fate:

- Biodegradation (Ready biodegradability)
- Adsorption in sewage sludge and soil [adsorption/desorption (batch equilibrium method)]
- Fate in water sediment systems (aerobic transformation in aquatic sediment systems)

Studies of Effects, to define the behavior of the drug in the environment:

- Algae, growth inibition
- Daphnia, reproduction
- Fish, early life-stage toxicity
- Sludge micro-organisms (activated sludge, respiration inhibition

Of these tests, only the biodegradation study may be waived. A study on the fate in water sediment systems will not be required for readily biodegradable compounds.

Expertise in environmental fate and ecotoxicology studies is essential when interpreting the results. At the end of Tier A, a predicted no-effect concentration (PNEC) is derived from the test results and the risk assessment performed. Phase II Tier A can take around 9-12 months, or longer for difficult substances. Some refinement to the PECsw is possible following Tier A, allowing the product to pass the risk assessment at this stage; however, it is likely that, in about 15% of cases, at least some of Phase II Tier B studies will be triggered, which will allow further refinements.

Phase II Tier B

Phase II Tier B may include seven further studies to examine the effects of the drug in the aquatic and terrestrial environments. These may include an investigation of the bioaccumulation in fish [required if the octanol/water partition coefficient at around pH 7 (log Pow) is ≥3], the effect on sediment-dwelling organisms (nearly always triggered based on results from the aquatic sediment fate study) and five terrestrial studies (fate in soil, effects on soil micro-organisms, plants, earthworms and the soil organism Collembola); these terrestrial studies are triggered less frequently. The Tier B studies can take another 9-12 months.

Once the data are available, a report is written to include the PBT assessment, the Tier A studies and any Tier B studies. At this stage, the overall risk to the aquatic and terrestrial environments is determined. Of particular importance, if the drug affects the endocrine system, further evaluation may be necessary. This would usually be identified from preclinical toxicology studies, or it may be evident from the mode of action and prescribed use of the drug, for example, or fertility treatments.

As ERA programs are both complex, experts in ERA regulations should be involved at every step of the process. This will ensure that studies are performed as expected by the various authorities, and advice is provided to study directors as the studies progress, including on whether Tier B studies are triggered. The report must be written by the expert whose CV is attached to the report to demonstrate relevant expertise.

Issues that Pharmaceutical Developers May Face

A full understanding of the guidelines is essential to carry out an ERA, and the first main issue that pharmaceutical developers are likely to face is a lack of experience of the regulatory requirements. Apart from some large pharmaceutical companies, which have their own dedicated ERA team, the challenge of understanding the requirements is often the responsibility of toxicologists or the regulatory affairs department.

As environmental testing is a key component of industrial and agrochemical testing, it is important to work with an expert ERA consultant who is familiar with the OECD Test Guidelines for all of the studies to be conducted, such as soil or sediment tests and has extensive experience in how to interpret the results of such studies. An expert ERA consultant can advise pharmaceutical developers on these results and their meaning in terms of the overall risk assessment.

Of particular focus for the pharmaceutical industry at the moment are drugs that have the potential to disrupt endocrine pathways. These require additional, often very extensive, assessment. The ERA supplier can provide support for these studies by acting as an intermediary with regulators, and, in this respect, may be able to ensure that only the most essential studies are performed. This has the advantage of reducing costs and speeding the drug's progress to market.

Key Considerations for the Selection of an ERA Supplier

A Focus on Regulatory Issues and Customer Service

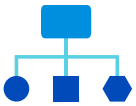
An ERA supplier needs to maintain close relationships with both the pharmaceutical developer and the global regulatory authorities to ensure they can advise on the drug developer's needs from a regulatory perspective. This brings the regulatory requirements to the forefront and bridges the gap in understanding between the authority and pharmaceutical developer.

Expert Support and Advice at Every Stage

Efficient contact and consultancy during all stages of the ERA process are critical. From an ERA supplier perspective, it is necessary to provide pharmaceutical developers with a clear understanding of what regulators require, and optimized study designs, that balance cost and the ethical use of animals. The ERA supplier should be able to coordinate all elements of the assessment and provide support from commencement to post-submission of the report. A comprehensive service will offer solutions to administrative and logistic challenges, in addition to the scientific expertise, to produce the report. This expertise could also save the pharmaceutical developer considerable costs, if it can be demonstrated early in the process that some of the studies can be waived.

Optimized Study Design and Execution

A capable ERA supplier will be able to develop optimized study designs, tailored to each pharmaceutical product's specific needs. They will be able to carry out all the environmental studies as part of a complete ERA, with consideration for the issues involved with each test, including higher studies, and for the relevant guidelines to ensure recognition of the test quality by authorities.



State-of-the-Art Methodologies

High-caliber facilities are fundamental in conducting high-quality studies; at a minimum, proficiency in principal methods of analysis should be expected, including mass spectrometry, liquid chromatography, liquid scintillation counting and carbon analysis, alongside experienced analytical staff to execute them.

Expertise in Action

Case Study 1: ERA Program for an Antidepressant Drug (Oral Dose 20 mg/day)
Phase I estimation of exposure in surface water: • PECsw: 0.1 µg/L → Phase II Tier A • Octanol/water partition coefficient ≥1,000 (log Pow ≥3) → fish bioaccumulation study
Phase II Tier A • Adsorption in sewage sludge: >10,000 → Phase II Tier B terrestrial studies • Ready biodegradability: not biodegradable → aquatic sediment study
Aquatic sediment study: • >80% in sediment, of which 30% was parent drug → sediment-dwelling organism toxicity study • Parent drug not persistent in aquatic sediment system • Two metabolites identified by mass spectrometry
Environmental effects: • Algal growth inhibition, Daphnia reproduction, and fish early life stage • Most sensitive species were fish; no effect at concentration of <0.1 µg/L • No effect on sludge micro-organisms
Risk assessment (PECsw refined with sales forecast data): • Surface water: failed → further evaluation • Groundwater: passed • Micro-organisms: passed
Phase II Tier B • Fish bioaccumulation: bioconcentration factor >2,000: designated as bioaccumulative • Sediment-dwelling organism toxicity: not toxic • Soil transformation study (four soils): not persistent • Soil micro-organisms: no effect • Plant growth (six species): no effect • Earthworm and Collembola: no effect
Risk assessment: • PECsw refined by considering metabolism in humans: failed • PECsw refined by considering kinetic modeling: failed • PECsw refined by considering fate in sewage sludge: passed • Sediment and terrestrial: passed
Conclusion This was a complex ERA program.

Case Study 2: ERA Program for a Generic Synthetic Steroid Hormonal Contraceptive, with Two Active Components (oral dose of both <1 mg/day)

Phase I estimation of exposure in surface water:

- PECsw: <0.01 µg/L for both components, but potential endocrine disruptors → Phase II Tier A plus full fish lifecycle study
- Octanol/water partition coefficient ≥1,000 (log Pow ≥3) → fish bioaccumulation study
- Cost estimated at >$2million
- Decision: obtain a waiver for the ERA program, using acceptable-quality data available in the public domain

Literature search:

- Around 800 publications found in an initial search
- 100 publications selected for review
- 50 publications selected as being of acceptable quality for assessing the environmental risk of the two synthetic steroids
- Position document produced

Phase II Tier A

- Adsorption in sewage sludge: <10,000 → no Phase II Tier B terrestrial studies
- Ready biodegradability: not biodegradable → aquatic sediment study
- Aquatic sediment study: both active components probably persistent

Environmental effects:

- Algal growth inhibition, Daphnia reproduction: no effect at concentrations >5 µg/L
- Full fish lifecycle study: demonstrated endocrine effects at <0.01 µg/L
- Environmental levels: the environmental exposure from this product would not be expected to result in a significant increase to the environmental concentrations already present in water bodies in the EU

Risk assessment (PECsw refined with sales forecast data):

- Surface water: failed → further evaluation
- Groundwater: passed
- Micro-organisms: passed

Phase II Tier B

- Fish bioaccumulation: bioconcentration factor <2,000: not bioaccumulative
- Sediment-dwelling organism toxicity: not toxic
- Risk assessment: both components designated as endocrine disruptors

Cost:

- Cost of producing the position document: <$35,000

Conclusion

It cannot be guaranteed that all attempts at waivers will be successful, but Labcorp can usually obtain waivers for some studies. In this case, the saving due to waiving studies was likely to be more than $2 million.

Summary

An ERA is an essential part of a development program when the compound in question is intended for human use. Before marketing authorization, the impact of all new drugs, as well as of generic compounds, on the environment must be assessed. A phased approach to ERA is conducted in the EU, according to EMA guidelines. A full understanding of the guidelines is essential when carrying out an ERA, and advice from an expert is often beneficial to clients at various stages of the program.

Your ERA supplier must possess extensive experience for a wide range of pharmaceutical products, including endocrine disruptors. Through in-depth understanding of the regulatory guidelines, as well as close relationships with pharmaceutical developers and the EU authorities, a capable ERA supplier can provide support and guidance at every step of the process, from optimized study design and execution to expert report writing and post-submission support.

About the Author

Dr. Francis Crawley has been working on pharmaceutical ERA programs for fifteen years. He has a good collaborative relationship with both the UK (Medicines and Healthcare products Regulatory Agency; MHRA) and German regulatory authorities; furthermore, he has assisted in providing two training visits for the MHRA (2011 and 2015). He has also been involved in discussions with pharmaceutical developers and regulatory authorities including both pre- and post-submission stages.

Dr. Crawley has provided regulatory advice on ERA requirements to more than 60 EU, U.S. and Japanese pharmaceutical companies on over 120 drugs or drug products. He has written the following reports:

- Standalone Phase I: 31
- Phase II Tier A: 35
- Phase II Tier A and Tier B: 11 (including two involving endocrine disruptors)
- US FDA: 12 (including one involving an endocrine disruptor)
- Position documents to waiver all or some studies: 25 (providing an overall saving for pharmaceutical developers of more than $16 million) including radiosynthesis

References

1. European Medicines Agency. Guideline on the environmental risk assessment of medicinal products for human use. EMA, 2006. www.ema.europa.eu/docs/ en_GB/document_library/ Scientific_guideline/2009/10/ WC500003978.pdf
2. European Medicines Agency. Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'. EMA, 2016. www.ema.europa.eu/docs/en_GB/ document_library/ Scientific_guideline/2016/06/WC500207858.pdf
3. U.S. Food and Drug Administration. Guidance for industry: environmental assessment of human drug and biologics applications. FDA, 1998. https://www.fda.gov/regulatory- information/ search-fda-guidance-documents/ environmental-assessment-human-drug-and-biologics- applications
4. U.S. Food and Drug Administration. Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity: Guidance for Industry. FDA, 1998. www.fda.gov/ downloads/Drugs/Guidances/UCM444658.pdf