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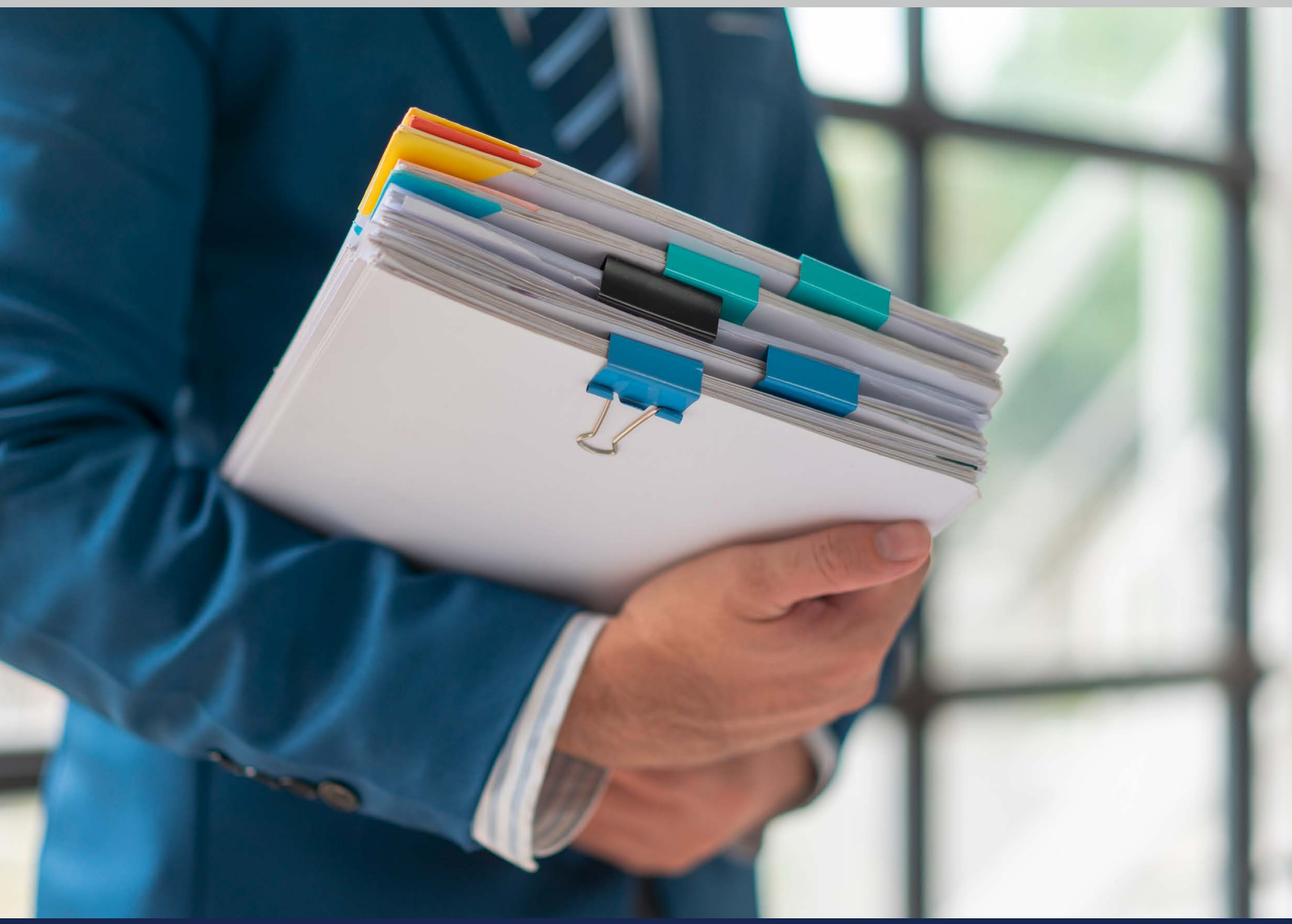

Environmental Risk Assessment

Legal Changes to Fortify ERA of Pharmaceuticals

Dr Angela Vogt-Eisele

Dear Reader

We are pleased that you are interested in this white paper.

The environmental impact of pharmaceuticals is gaining increasing attention, with new regulations on the horizon that could significantly affect the pharmaceutical industry.

The proposed directive on medicinal products for human use aims to enhance environmental sustainability by introducing stricter requirements for Environmental Risk Assessments (ERA) and risk mitigation measures. This whitepaper offers a comprehensive overview of the forthcoming legislative changes, highlights key differences from Directive 2001/83/EC, and provides valuable insights into how pharmaceutical companies can navigate these new challenges efficiently.

We wish you many new insights while reading.

About the author

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Dr Angela Vogt-Eisele has over 10 years of experience in the pharmaceutical industry, supporting non-clinical and clinical development programs. She specialises in preparing and managing dossiers, paediatric investigation plans, orphan drug designations, environmental risk assessments, and regulatory documents. She regularly communicates with health agencies during scientific advice meetings.

Legal Changes to Fortify ERA of Pharmaceuticals

Awareness of the risks associated with the impact pharmaceuticals have on the environment is rising [1-6], with several initiatives ongoing to limit and mitigate these risks [7-10]. Among the most consequential proposals for pharmaceutical companies are changes to the current legislation in the proposed new directive on medicinal products for human use [11]. Directive 2001/83/EC will eventually be repealed and replaced with the new directive.

In the proposal for the new directive, which was presented to the European Parliament in April 2024, a primary objective is to "make medicines more environmentally sustainable". With that in mind, a number of proposed changes relative to Directive 2001/83/EC concern the evaluation and mitigation of environmental risks associated with medicinal products for human use.

These success factors are essential for creating Development Safety Update Reports (DSUR), Risk Management Plans (RMP), and Periodic Safety Update Reports (PSUR), which are required throughout a product's lifecycle. These key pharmacovigilance documents are needed from the development stage through to post-marketing. DSUR focuses on monitoring safety during development, RMP outlines the plan to manage of risk, and PSUR evaluates the product's benefit-risk balance in the post-approval phase. A critical aspect is meeting the growing regulatory demands, from the initial characterisation of the safety profile to the benefit-risk assessment at the time of application for marketing authorisation and in post-marketing phase. This ultimately determines the marketability of medicinal products.

Proposal for a new directive

The following key changes are notable in the proposed directive [11]:

- While Directive 2001/83/EC demands the submission of an Environmental Risk Assessment (ERA) with the submission of marketing authorization application (MAA), results of the ERA must not constitute a criterion to refuse or delay marketing authorization. In contrast, the proposed directive allows for the MAA to be refused if the ERA is incomplete or not sufficiently substantiated, or if risk mitigation measures appear insufficient [11]. This practice is already applied in the United States, where an inadequate environmental assessment (EA) is a reason for refusal of MAA [12].
- Under the current directive, a well-defined set of tests has to be performed to assess potential risks to distinct environmental compartments, such as aquatic, soil, sediment and sewage. Depending on the outcome, additional tests may be demanded. The scope is broadened in the new framework, also addressing antimicrobial resistance.
- Mitigation of environmental risks in the current directive was limited to the addition of appropriate wording in the prescribing information. According to the proposed directive, more comprehensive measures to avoid or limit emissions of pollutants to air, water, and soil are to be proposed by the applicant, although the document does not elaborate on the nature of such measures.
- While the ERA is a one-time assessment during MAA under the current legislation, regular updates are demanded in the proposed directive, and the marketing authorization holder (MAH) is held responsible for timely implementation of any relevant new information, much like pharmacovigilance requirements [13].
- For medicinal products authorized before 30 October 2005, i.e. before submission of an ERA became mandatory, the agency will set up a risk-based prioritization program for ERA submission or updates by MAHs.
- Importantly, a monograph system is planned, where available environmental information on specific active substances is collected and can eventually be referred to by other applicants.

The new guideline for ERAs has already come into effect

Ahead of these upcoming changes, a revision of the "guideline on the environmental risk of human pharmaceuticals for human use" [14] came into effect in September 2024. The initial version of the guideline, which was published in 2006 and covered 12 pages, has been replaced by a 64-page document with more detailed descriptions, information previously referred to from other sources, clarifications, and overview tables.

Much remains the same with both versions of the guideline, including:

- Two independent parameters are regarded in Phase I: One depending on intrinsic properties of the active substance (the octanol-water coefficient for the hazard assessment), the other depending on the calculated amount entering the environment (Predicted Environmental Concentration for the risk assessment). Both parameters have independent action limits and trigger the performance of two sets of tests, the assessment of persistence, bioaccumulation and toxicity (PBT) and Phase II testing, respectively. [14]
- Phase II testing starts with an initial set of tests, and additional tests may be triggered by its results. Tests and action limits remain similar to the initial version of the guideline, although the hierarchy and organization of the test set has been somewhat altered.
- Phase II Tier A tests are still followed by Tier B tests in the environmental compartments where a risk was identified.
- Tests should be performed according to defined OECD test guidelines in a GLP-certified laboratory.
- Upon finalization of the test sets in phase II and PBT, results are cumulatively evaluated and result in the insertion of a defined wording in the package insert and Summary of Product Characteristics (SmPC), corresponding to any identified risks, as a mitigation measure.

Nevertheless, despite the overall comparable approach, the revision of the guideline also resulted in several profound changes:

First and foremost, the possibility of waiving the conduct of ecotoxicological studies for generic products (which was not clear-cut in the preceding version either, but nevertheless accepted in most instances) has been removed. A full assessment, including a complete set of study reports, is now required. This is a relevant issue for most generic companies, as carrying out the required studies adds significant costs. Depending on the molecule, it may, however, be possible to cover part of the required studies by referring to scientific literature or by requesting data from competitors, although this can be difficult to negotiate.

Second, a clear definition of compounds with a "specific toxicological profile" requiring a tailored assessment (i.e. a study set deviating from the standard one) is provided in the new guideline and a clear definition of the tailored assessment is provided for each specific case.

A third difference to the previous version is a clear statement from the agency that repetition of studies is not desired, prompting the applicant to use available literature sources wherever possible (although most MAHs don't need much prompting as this approach saves a lot of time and resources!).

Fortunately, there are several options that would allow MAHs to waive or reduce the required study set. In addition to covering part of the requirements through references to the literature, products may be exempted from studies based on detailed information on the epidemiology of the target indication, treatment regimen or specific properties of the drug substance.

Conclusion

While the future directive [11] is awaited with some apprehension, the revised version of the guideline on the ERA of medicinal products for human use [14] already anticipates some of the pending changes. Considering the information available so far, the investigation and mitigation of environmental risks associated with pharmaceuticals will likely play a larger role in the future, adding complexities for pharmaceutical companies.

Working with experts who understand the ERA requirements and are familiar with the views of the regulatory authorities can help to simplify the process.

Further Information

For more information on PharmaLex's expertise on ERA, please visit the following website: https://www.pharmalex.com/thought-leadership/blogs/legal-changes-to-fortify-environmental-risk-assessment-of-pharmaceuticals/

To listen to PharmaLex's podcast on ERA, please visit the following website: https://www.pharmalex.com/thought-leadership/podcasts/environmental-risk-assessment-and-its-growing-importance-in-the-german-pharma-strategy/

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