

## Sound Strategies for Complying with the Final EMEA Human Pharmaceutical Environmental Assessment Guidelines

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### Introduction

Gradient Corporation has been assisting pharmaceutical clients for several years to keep abreast of global environmental regulatory changes, monitor developments in the European Medicines Agency (EMA) environmental risk assessment (ERA) framework, and track the evolving state of science on topics such as endocrine disruption. This experience has allowed us to identify a number of important strategic elements to consider when defining testing and assessment steps necessary for preparing sound science-based ERAs for active pharmaceutical ingredients (APIs). Based on our experience, the careful examination, consideration, and appropriate inclusion of these strategic elements into a company's API environmental testing and assessment approach leads to scientifically sound decision-making, while achieving superior efficiency in the use of environmental compliance budgets.

**Define your corporate strategy before you select your test and assessment procedures.** You can optimize your testing and assessment resources by defining your corporate priorities before you begin. Some companies might be comfortable submitting an ERA that uses sound data collected in their in-house laboratories for other purposes (e.g., hydrolysis data generated to establish the API's shelf-life), at the risk of potentially being asked to submit a standard OECD GLP study later. Other companies might wish to conduct a wider range of standard GLP tests immediately, to proactively develop a robust database for their products.

**Define your full range of environmental data needs before developing a testing plan for EMEA compliance.** For instance, your company might find it beneficial to use environmental data to make informed decisions regarding industrial wastewater treatment

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processes, regardless of whether manufacturing and formulating is done in-house or by toll manufacturers. Some of the tests and assessment procedures used in EMEA ERAs can also be used to support risk-based effluent concentrations at API manufacturing facilities or to identify promising industrial wastewater treatment technologies. Preferentially selecting tests that can be leveraged in multiple ways saves resources.

**Prepare an environmental testing program that begins more than a year before your EMEA submission.** While testing requirements for some APIs can be minimal, many APIs will need to undergo a suite of tests that takes months, and that sometimes will trigger subsequent tests that can also take months. The process requires significant lead time to avoid having the ERA delay an API's dossier submission.

**Be aware that the European "categorical exclusion" is not as simple as in the past.** A large number of APIs will require full ERAs, because the exclusion is dose-based and not mass-based. Unlike in the US, where a mass-based exemption from the need to perform a full assessment applies (i.e., no ERA is required for APIs sold at a rate less than 44,000 kgs/yr), in the EU, the exclusion is dose-based, which accounts for lifestyle and demographic variabilities among member EU nations. As a result, a comprehensive assessment must be conducted for all APIs for which the default maximum API dose is greater than 2 mg/day. Furthermore, that exclusion does not apply if the API is hydrophobic, because a persistent, bioaccumulative and toxic (PBT) assessment is required for any API with a log K<sub>ow</sub> (octanol-water partition coefficient) greater than 4.5, regardless of its dose. The new guidelines apply to all new APIs, including over the counter medications and those administered via any route (e.g., oral, injectable, inhaled), and when there is a change in API use that would lead to greater potential environmental exposures (e.g., previously approved APIs to be used to treat a new disease).

**Prepare to perform both a PBT assessment and a standard ERA.** Any API with a log K<sub>ow</sub>

(octanol-water partition coefficient) that exceeds 4.5 must undergo a PBT assessment, which has different testing and assessment requirements from a standard ERA. It is important to consider both the PBT and standard ERA processes simultaneously, to avoid choosing tests that are acceptable for one approach but not the other.

**Substitute modeled data for measured data where appropriate.** The outcome of some laboratory tests recommended by EMEA can be reasonably predicted using relatively simple models. Modeling results can then be used to determine the need for undertaking costly laboratory tests. For example, the EMEA guidance recommends undertaking the OECD 308 test as a means for determining if sediment toxicity testing is necessary. The results of the OECD 308 test can be reasonably modeled; hence, for many APIs the decision to run a sediment toxicity test and assess the API's safety in sediment can be made with significant cost and time savings by substituting modeled results for the OECD 308 test.

**Be aware that data collected in the past may not fulfill new recommendations.** If you are submitting an ERA for an older API that will be marketed for new and expanded uses, older data that were previously adequate may no longer be sufficient. For example, acute aquatic toxicity data were previously acceptable, but the current EMEA process requires chronic aquatic toxicity testing.

**Prepare for complications if your API is ionizable.** The acid/base chemistry of APIs can complicate the assessment process. EMEA guidelines do not prescribe a testing and assessment methodology for compounds whose properties change dramatically as the pH of the receiving water changes. If your API's solubility, partitioning, or toxicity changes over the environmentally relevant pH range, case-by-case choices for testing conditions and test interpretation will be required to prepare a sound ERA.

**Expert judgment is required for appropriately assessing endocrine effects.** The EMEA guidance requires that a customized assessment be undertaken by an “Expert” if your API is likely to be an endocrine disruptor. Since standardized tests for endocrine disruption effects are still under development, it is critical to review the available data for the API to determine if endocrine disruption effects are anticipated, and if so, to develop a scientifically sound effects assessment approach.

**If you have multiple APIs in the pipeline, consider developing a standard protocol for testing and assessment.** The use of a consistent, well-documented approach to plan your standard testing and assessment strategy and timeline can help consistently address all of the issues listed above.

Overall, careful consideration of the elements identified above will lead to a cost-effective and scientifically sound API environmental testing and assessment framework.

## About the Authors

Dr. Saxe has expertise in evaluating and modeling the environmental transport, transformation, fate, and ecological bioavailability of chemicals, including designing and critically evaluating related environmental analytical chemistry efforts. The majority of her work in recent years has focused on the fate and potential effects of chemicals in consumer products. She has conducted site-specific ecological and human health risk assessments, and has prepared stand-alone fate and transport analyses to support clients’ strategic interests. She has provided public testimony and taken part in agency negotiations to present findings. Before joining Gradient, Dr. Saxe worked in the U.S. EPA’s Office of Research and Development creating a software tool to allow the potential environmental impacts of chemical processes to be proactively scored and compared. She regularly presents scientific findings at professional conferences and authors book chapters and peer-reviewed articles in her areas of expertise.

Mr. Sharma, a Licensed Professional Engineer with over 18 years of consulting experience, specializes in evaluating chemical exposures and human health/environmental risks associated with waste sites and products, multi-media mathematical modeling applied to hydrogeologic investigation and waste site remedial design, modeling VOC vapor intrusion into buildings, and providing litigation support. He has successfully applied these skills for assessing environmental risks associated with pharmaceuticals and personal care products; evaluating risks to ecological systems due to industrial legacy operations; and developing risk-based cost-effective remedial solutions at a variety of waste sites and chemical plants. Mr. Sharma has worked extensively with chlorinated solvents, NAPLs, pesticides, metals, petroleum hydrocarbons, and mercury. He has provided public testimony, served as an expert witness on a variety of cases, and negotiated sound-science based solutions with regulators around the world. Mr. Sharma routinely presents scientific papers at conferences, publishes in peer-reviewed journals, and serves on risk assessment regulatory review panels.