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# Proactively managing the environmental risks associated with the patient use of human medicinal products

## An extended Environmental Risk Assessment (eERA) proposal by the European pharmaceutical industry associations EFPIA, AESGP, and Medicines for Europe

# EXECUTIVE SUMMARY

**EFPIA, AESGP and Medicines for Europe are committed to ensuring the environmental safety of their Medicinal Products (MPs) across the product lifecycle.**

In the EU a prospective Environmental Risk Assessment (E.R.A.) is required since 2006 (CPMP/SWP/4447/00, 2006[1]) when a marketing authorisation application (MAA) is submitted for a new MP to be placed on the market or where there is potential for significant increase in environmental concentrations as a result of modifications to existing marketing authorisations (MAs) (e.g. addition of new indications). Medicinal products approved prior to this date had no requirement for E.R.A.s.

The E.R.A. is currently based on the use of an individual MP and therefore does not account for multiple MPs containing the same Active Pharmaceutical Ingredient (API), all of which contribute to the overall environmental burden with respect to Pharmaceuticals in the Environment (PIE).

Furthermore, the current legislation does not permit the automatic cross-referencing of environmental data and E.R.A.s (unlike pre-clinical and clinical data). The transparency and accessibility of environmental data in the public domain is inconsistent.

Additionally, there is a non-equitable burden on individual companies to provide data for those APIs for which data is not available due to being approved prior to 2006. Such challenges have been shown to lead to disproportionate resource burden, conflicting E.R.A. conclusions for the same API, and duplicative demands on data generation with associated bioethical issues.

[1] Guideline on the environment risk assessment of medicinal products for human use; EMEA/CHMP/SWP/4447/00 corr 2; 01. June 2006

The extended E.R.A. (eERA) approach proposed here by the three industry trade associations (EFPIA, AESGP and Medicines for Europe) is designed to address these challenges and strengthen the E.R.A. process in the EU. In summary the eERA aims to provide the following benefits:

- An API based E.R.A. which better reflects the risks posed to environment from patient use
- Strengthen the industry's commitment to conduct robust and risk-based E.R.A.s without compromising environmental protection or patient access to medicines
- Provision for the ability to automatically cross-reference E.R.A. data in marketing authorisation applications
- Provide a mechanism for risk identification, refinement, and management during the MAA evaluation process
- Provide clarity on appropriate well-defined follow-up responsibilities for E.R.A.s with no need for independent and duplicative risk identification and prioritisation processes under different legislations (e.g. Water Framework Directive)
- Updates to the E.R.A. across the life cycle of the API in each MP in which it is contained that will ensure that each E.R.A. reflects the latest environmental information
- A focus on risk that reduces the burden on regulators (i.e. oversight) and industry
- Reduction in the duplication of testing, delivering improved E.R.A. consistency, proportionate use of testing resource, and bioethical benefits
- Suggestions for mechanisms to increase the transparency of, and access to, E.R.A. data

## BACKGROUND AND OBJECTIVES

The risk of PIE is currently managed through the implementation of a prospective E.R.A. (CPMP/SWP/4447/00 Corr 2", page 3)[1] which is produced as part of a MAA in the EU. The environmental risk posed is the result of the intrinsic hazards of the API, their use and exposure in the environment. The knowledge and understanding of both the intrinsic hazards and exposure can change over time, as the science evolves. It is therefore important to not only consider environmental risks at the time of submission of a MAA but also post-authorisation. Moreover, the risk of an API should be evaluated across all MPs containing the same API to demonstrate its environmental safety.

Recently, a number of publications such as, the Pharmaceuticals Strategy for Europe[2], the strategic approach to PIE[3], as well as the draft revision to the E.R.A. guideline[4], have begun to set the strategic regulatory direction in the EU. These publications suggest both legislative and non-legislative approaches to address concerns about the risk posed by the presence of pharmaceuticals in the environment: e.g., increased E.R.A. requirements for off-patent APIs, increased consideration of academic research studies in the E.R.A., increased regulatory oversight for groundwater-related exposure and extended producer responsibility, shared E.R.A. expertise and collaboration between EMA and EU Member States, and increased transparency of, and access to, E.R.A. data.

However, it is important that all stakeholders acknowledge that all medicinal products play a critical role in the provision of treatments to address patients' needs and that environmental risk needs to be considered in this context (e.g. EMEA/CHMP/SWP, 2018[5]): "*...in any event this* [environmental] *impact should not constitute a criterion for refusal of a marketing authorisation"*; and Strategic Approach to PiE, 2020: *"... future initiatives in the field of the environmental impact of pharmaceuticals should be ... making sure that safety and efficacy still remain key priorities for patients' access to pharmaceutical treatments"*).

The current EU E.R.A. approach (European Medicines Agency, 2006[6] & European Medicine Agency, 2016[7]) for human medicinal products has been in force since 2006. This has provided a solid foundation to build towards a new revised framework where the risks of pharmaceuticals in the environment can be effectively managed in a more transparent and inclusive way without compromising either environmental protection or patient access. To this end the Association of European Self-Medication Industry (AESGP), European Federation of Pharmaceutical Industry Associations (EFPIA) and Medicines for Europe have developed a holistic approach to the environmental assessment of human medicinal products called Eco-Pharmaco-Stewardship (EPS)[8]. Within this EPS initiative, AESGP, EFPIA and Medicines for Europe propose an extended Environmental Risk Assessment (eERA) to formally capture post-approval commitments, periodic environmental updates, prioritisation of "legacy" APIs (APIs in MPs approved for use pre-2006) for tailored E.R.A.s, and where required, environmental risk refinement and risk resolution.

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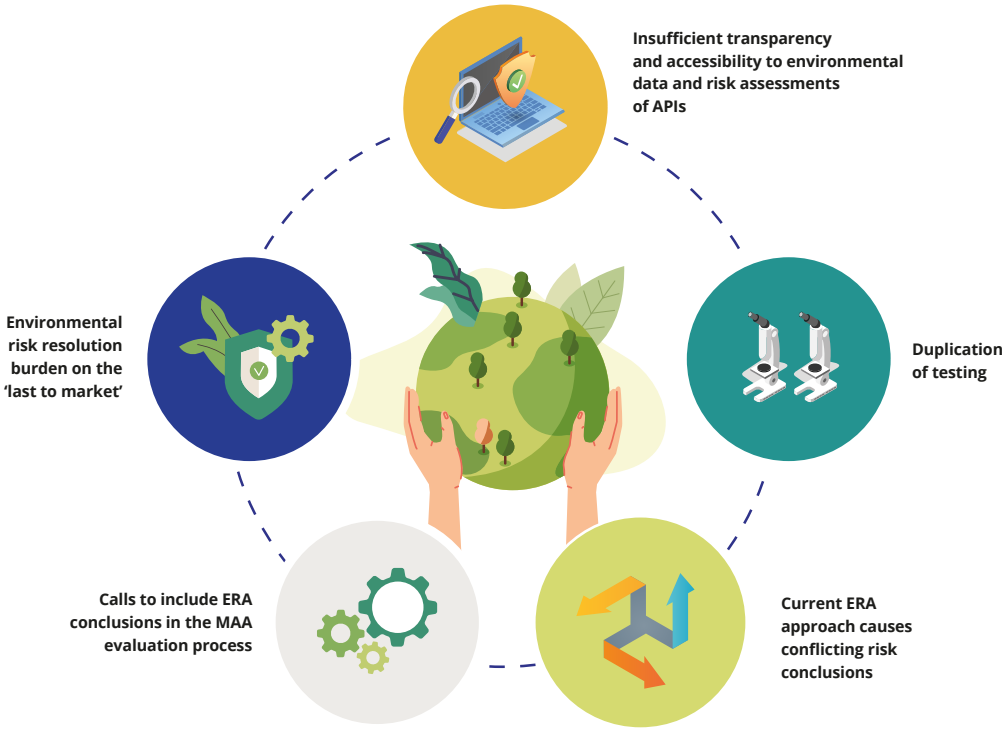
[2] Caldwell https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en
[3] https://ec.europa.eu/environment/water/water-dangersub/pharmaceuticals.htm
[4] https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use
[5] EMEA/CHMP/SWP/4447/00 Rev. 1, 15 November 2018
[6] European Medicines Agency (EMA) (2006/2015): Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), 01 June 2006, EMEA/CHMP/SWP/4447/00 corr 2
[7] European Medicines Agency (EMA) (2016): Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use', 26 May 2016, EMA/CHMP/SWP/44609/2010 Rev. 1
[8] https://www.efpia.eu/media/636524/efpia-eps-brochure_care-for-people-our-environment.pdf, https://aesgp.eu/eco-pharmaco-stewardship https://www.medicinesforeurope.com/wp-content/uploads/2016/03/EPS-PILLAR-3_EXTENDED-E.R.A._V3.compressed.pdf

The pharmaceutical industry and regulators have a shared goal, to deliver medicinal products to patients whilst minimising the impact of pharmaceuticals in the environment. We are confident that the industry's eERA initiative will address the issue of data availability and accessibility. The pharmaceutical industry is partnering with the European Commission through the Innovative Medicines Initiative (IMI) projects (iPiE[9], PREMIER[10]) to develop tools and models to support the prioritisation of APIs for a tailored or targeted E.R.A. where insufficient data exist to conclude on environmental risk. These projects help focus efforts of industry and regulators on those APIs and MPs that pose the greatest potential environmental risk and impact. The availability of these tools and models may also be used to include environmental considerations in the development of new, innovative candidate APIs.

The current MP-based approach to managing environmental risks has several issues associated with it in practice which are discussed below:




## Insufficient transparency and accessibility to environmental data and risk assessments of APIs

Currently, there is a defined set of environmental data available for each newly developed API contained in a MP for which a new marketing authorisation became available after the year 2006. After that date the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2; 01 June 2006[11]) came into force. Furthermore, data does exist for many APIs contained in MPs already marketed before this guideline came into effect as the E.R.A. requirement is applicable for each new MAA. Data also exist for APIs if tailored E.R.A.s were conducted to address specific mode of action related concerns (e.g. risks associated with APIs that are designed to be endocrine active; e.g. Länge et al., 2001[12]; Williams et al., 2007[13]; Panter et al., 2012[14]).

[9] https://www.imi.europa.eu/projects-results/project-factsheets/ipie#:~:text=The%20goal%20of%20iPiE%20is,the%20environmental%20impact%20of%20medicines
[10] https://imi-premier.eu/
[11] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf
[12] Lange et al. 2001. Effects of the synthetic Estogen &èa- Ethinylestradiol on the life-cycle of the fathead minnow (Pimephales Promelas). Environmental Toxicology and Chemistry, Vol. 20, No. 6, pp. 1216–1227, 2001
[13] Williams et al., 2007 Evaluation of the reproductive effects of tamoxifen citrate in partial and full life-cycle studies using fathead minnows (Pimephales promelas) - PubMed (nih.gov)
[14] Panter et al., 2012 Effects of the anti-androgen, bicalutamide, in a reduced life-cycle study with the fathead minnow (Pimephales promelas) - ScienceDirect

Whilst E.R.A.s and their supporting physico-chemical, ecotoxicity and environmental fate and behaviour data exist for many APIs, the transparency and accessibility of these E.R.A.s and their supporting data to key stakeholders and the public is limited and could be improved. The level of environmental data associated with a medicinal product presented in (European) Public Assessment Reports (EPARs & PARs) can be quite variable and its content is focused towards the regulatory science community and not the broader environmental stakeholder community. This holds true, e.g., for Predicted Environmental Concentrations (PECs) and Predicted No Effect Concentrations (PNECs) which are parameters used to assess the risks in various environmental compartments.

The lack of transparency and accessibility to environmental data associated with APIs does have the potential to undermine stakeholder confidence in regulatory oversight, as absence of data could be confused with absence of sufficient regulation, which is not the case. This lack of transparency of the data can lead to a misplaced assumption that presence of trace levels of pharmaceuticals poses a risk to the environment. Analysis of available data, using EU consumption data and worst-case exposure scenarios (100% patient use, no metabolism and no removal in wastewater treatment) demonstrates that any potential environmental risks are limited in nature (Gunnarsson et al., 2019[15]). The increased availability of measured environmental concentrations (MECs), through environmental monitoring studies, coupled with the lack of transparency of publicly available PNECs is intensifying stakeholder concerns associated with the presence of pharmaceutical residues, often at trace levels (low ng/l), in the environment.

## Duplication of testing

The lack of data transparency and accessibility can lead to further challenges. Currently, each marketing authorisation holder (MAH) must provide an E.R.A. containing the full set of data requested in the E.R.A. guideline. This EU requirement is critical considering that medicinal products can have multiple marketing authorisations (MAs) owned by different MAHs.

As a consequence, each MAH could be obliged to generate a full set of data for the same API. This does result in the duplication of testing, including some vertebrate studies (e.g. Straub et al., 2019, Caldwell et al., 2019) which poses bioethical concerns. Furthermore, duplicate tests lead to varying results for identical APIs (see next section). None of these are beneficial to the E.R.A.s and understanding of the potential hazards or risks of APIs. In fact, duplication takes valuable time and resource that could be used to address APIs where insufficient data currently exist to conclude on environmental risk. The lack of a mechanism for applicants to automatically-reference existing environmental data and associated E.R.A.s, means that there is a barrier to the effective sharing of data that needs to be addressed, especially where reliable and relevant data are known to be available.

Regulatory processes and procedures need to be revised for MPs to allow the automatic-referencing of environmental data without reliance on letters of access, similar to preclinical and clinical data, to avoid unnecessary duplicative testing and improve consistency.

[15] Gunnarsson et al., 2019 Pharmacology beyond the patient – The environmental risks of human drugs - ScienceDirect

## Current E.R.A. approach causes conflicting risk conclusions

The unnecessary repetition of tests results in duplication of data and may cause the creation of multiple redundant E.R.A.s or may even lead to divergent E.R.A.s, which will inevitably lead to inconsistent estimations of PNECs and PECs. This ultimately leads to different conclusions in E.R.A.s of the same API. A further confounding factor is that the E.R.A.s are currently MP-based and thus may fail to potentially account for multiple MPs on the market which contain the same API. Consequently, the MP-based approach may lead to inconsistent E.R.A. conclusions for different MPs with the same API depending on the use profile. This in turn leads to the potential for differential labelling and/or derivation of mitigation measures for MPs which contain the same API and therefore should have the same intrinsic risk profile.

The environmental hazard and risk of APIs is becoming a more important factor for considerations for both Health Care Professionals (HCPs) and patients. Conflicting E.R.A. conclusions unavoidably lead to confusion and misleading decision-making regarding patient access to MPs.

## Calls to include E.R.A. conclusions in the MAA evaluation process

There are increasing calls to integrate environmental hazard and risk considerations into the marketing authorisation evaluation process, with a focus on the benefit-risk analysis [EU Commission 2019[16], OECD 2019[17], HCWH et al 2020[18]]. This has the potential to have significant patient and societal impacts, as access to medicinal products could be delayed.

It should be recognised that E.R.A.s conducted according to the current E.R.A. guideline are based on unrealistic worst case emission estimates. E.R.A.s are based on a number of conservative assumptions such as, 1% market penetration of a MP (which is not reached for 95% of MPs), maximum daily dose (which is not necessarily relevant in all cases for either dose, or frequency of use), no patient metabolism (which is unrealistic for the APIs in many MPs), and absence of removal in sewage treatment (through biodegradation or partitioning, which is unrealistic for APIs in many MPs). Thus, many E.R.A.s clearly overestimate the true emissions and potential risks of APIs in the environment. Despite this fact, the PEC/ PNEC ratio (i.e., risk quotient (RQ)), is <1 in most cases indicating low or insignificant risk. The limited number of APIs that have a RQ > 1 are often based on unrealistic worst-case assumptions lacking a realistic refinement.

Risk refinement measures, often conducted as part of a post-approval commitment, usually address environmental concerns associated with any MP with an RQ≥1. The ability to refine potential risks post-approval recognises that MPs may have low market penetration (I.e. low environmental exposure) and consequently a low environmental risk immediately after approval of the MAA for MPs containing newly developed APIs.

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[16] Strategic approach to pharmaceuticals in the environment
https://www.europarl.europa.eu/doceo/document/TA-9-2020-0226_EN.pdf

[17] OECD 2019 Pharmaceutical Residues in Freshwater Hazards and Policy Responses
https://www.oecd.org/health/pharmaceutical-residues-in-freshwater-c936f42d-en.htm

[18] HCWH + other GMO Joint Position paper on the Pharmaceutical strategy for EU
https://noharm-europe.org/sites/default/files/documents-files/6473/2020-07-13_Joint-position-paper-EU-Pharma-strategy.pdf

Generally implemented options for refinement of risk assessments include, for example, the use of consumption data and removal in sewage treatment. It should however be noted that E.R.A.s will generally be refined only to a degree whereby the RQ is <1 (i.e. indicating low or insignificant risk) which is the primary aim within the submitted MAA(s). However, with varying levels of risk refinement being applied to achieve a RQ<1 for different MPs, it can then be difficult to draw comparisons between E.R.A.s for the same API, or between different APIs from the same therapeutic class.

Recent evaluations of E.R.A.s have demonstrated that the large majority of APIs represent low or insignificant environmental risk, with potential risks being limited to a few mode-of-actions and APIs with high lipophilicity, even under worst-case assumptions (e.g. Gunnarsson et al 2019[15]).

Taking into account existing data and evaluations of API risks, calls to incorporate E.R.A.s in the risk-benefit analysis for MPs appears to be unjustified. Patient access could be impacted based on theoretical risks, resulting from unrealistic and conservative E.R.A.s, that could be refined with additional data and never be manifest through patient use. There are concerns from industry and patient groups, that access to treatments, that bring significant health benefits to patients and society, could be delayed or denied, if unrealistic worst case environmental risks would be communicated without appropriate context. That said, environmental risks need to be updated and refined in light of emerging science, and PEC values can be compared to emerging MEC data; this is central to the proposed eERA model.

The eERA approach discussed in this document continues to place patient access as the primary driver. Current provisions for environmental risk refinements and mitigation strategies, conducted post-approval should be maintained and strengthened, to ensure patient access does not compromise environmental protection.

## Environmental risk resolution burden on the ‘last to market’

For a MP containing an API in use prior to the requirement for an E.R.A. in 2006, the requirement for an E.R.A., the supporting data and any risk resolution measures, falls on each company submitting a new MAA. The potential for environmental impact of these APIs is not driven solely by these newly launched medicinal products. Instead, it is likely that any potential environmental impact is driven by the use of existing MPs. Thus, the reliance on the ‘last to market’ having to generate the data and risk assessment is disproportionate. This could be an additional barrier to innovation for the use of existing MPs to treat new or rare indications.

The draft E.R.A. guideline, also proposes wider consideration and evaluation of published literature in the E.R.A.. Whilst important, this has the potential to further increase the regulatory data requirements for APIs and needs to be managed accordingly to ensure that new or emerging science is captured and assessed in a way that increases confidence and certainty within the E.R.A..

# Industry proposal for an extended environmental risk assessment

It is the aim of this document to show how the eERA approach can proactively address all these challenges from the approval and use of a MP including: (i) the provision of an E.R.A. at the point of the initial MAA for an innovative medicine, (ii) the update of that E.R.A. prior to the loss of data exclusivity (and entry into the market of new MAs), (iii) the increased transparency and accessibility of data to help with ongoing environmental risk management over the lifetime of the API, and (iv) prioritising and addressing risks associated with APIs with insufficient data to conclude on environmental risk. The eERA approach also highlights the need for increased expertise and co-ordination for regulatory reviews at EU Member State levels, as well as an obligation on industry to update E.R.A.s, to work collaboratively and to prioritise and address key data gaps for established APIs.

The eERA framework has been developed with three situations in mind (Figure 1). Situations 1 & 2 are for APIs marketed post-2006 and addresses environmental risks based on total API use as well as MP specific use. Situation 1 describes specifically newly developed, i.e. patented, APIs, including potential post-approval risk refinements and updates to ensure proactive and ongoing management of API-related environmental risks prior to loss of data exclusivity. Situation 2 deals with APIs where exclusivity has expired. It is focused on ensuring that generic market entry for existing indications and new indications for MPs, containing that API, does not compromise environmental protection. Situation 3 describes the options for legacy APIs (i.e. those APIs already in use prior to 2006) that have insufficient data to conclude on environmental risk. Tools are being developed via the IMI iPiE and PREMIER projects that will help to prioritise these legacy APIs for tailored E.R.A.s.

The eERA proposal recommends that an E.R.A. expert group is established to provide regulatory oversight across all three situations that captures centralised, decentralised, mutual recognition and national marketing applications to proactively manage environmental risk throughout the product and API life cycle that includes a mechanism to review E.R.A. updates

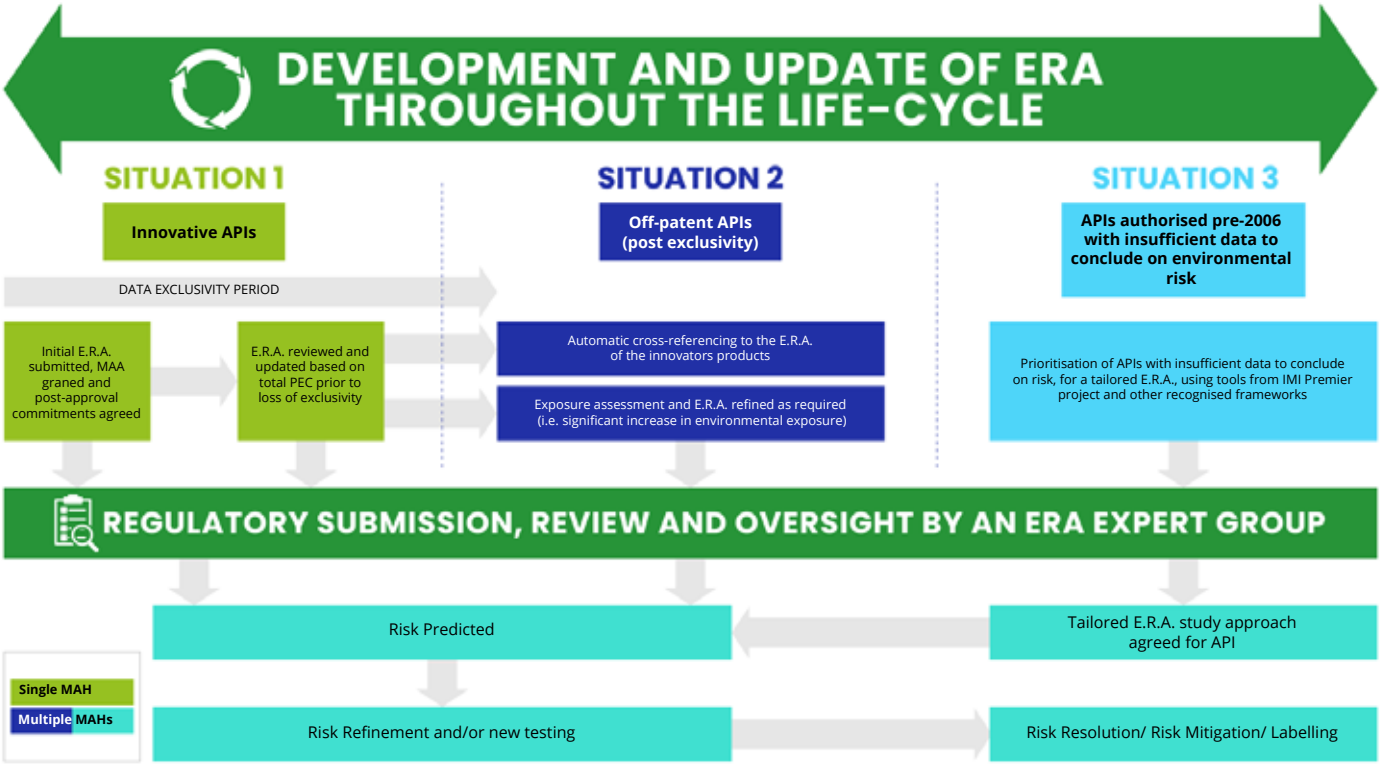



**Figure 1:**
Proposed eERA approach ensuring the update, oversight and management of the environmental risks of human medicinal products resulting from patient use. Details and the drivers for each specific scenario are covered in the text.

# SITUATION 1: Innovative APIs

**Situation 1 describes the generation and the proactive ongoing update of E.R.A.s for innovative, patented, medicinal products at the MP and API level during their period of exclusivity (see Figure 2).**

## Pre-submission Decisions

During development of a new API or medicinal product it is the applicant's responsibility to generate an E.R.A. according to the current E.R.A. guideline to be submitted with the MAA. In some cases, and if timing allows, it may be advantageous to have discussions with the relevant authorities in pre-submission meetings to agree on testing requirements where there may be specific mode of action considerations, or discuss the nature and availability of environmental data and E.R.A.s at time of MAA submission. There are two scenarios recognized in situation 1 for submission of new E.R.A.s. These are detailed in the paragraphs below and Figure 2.

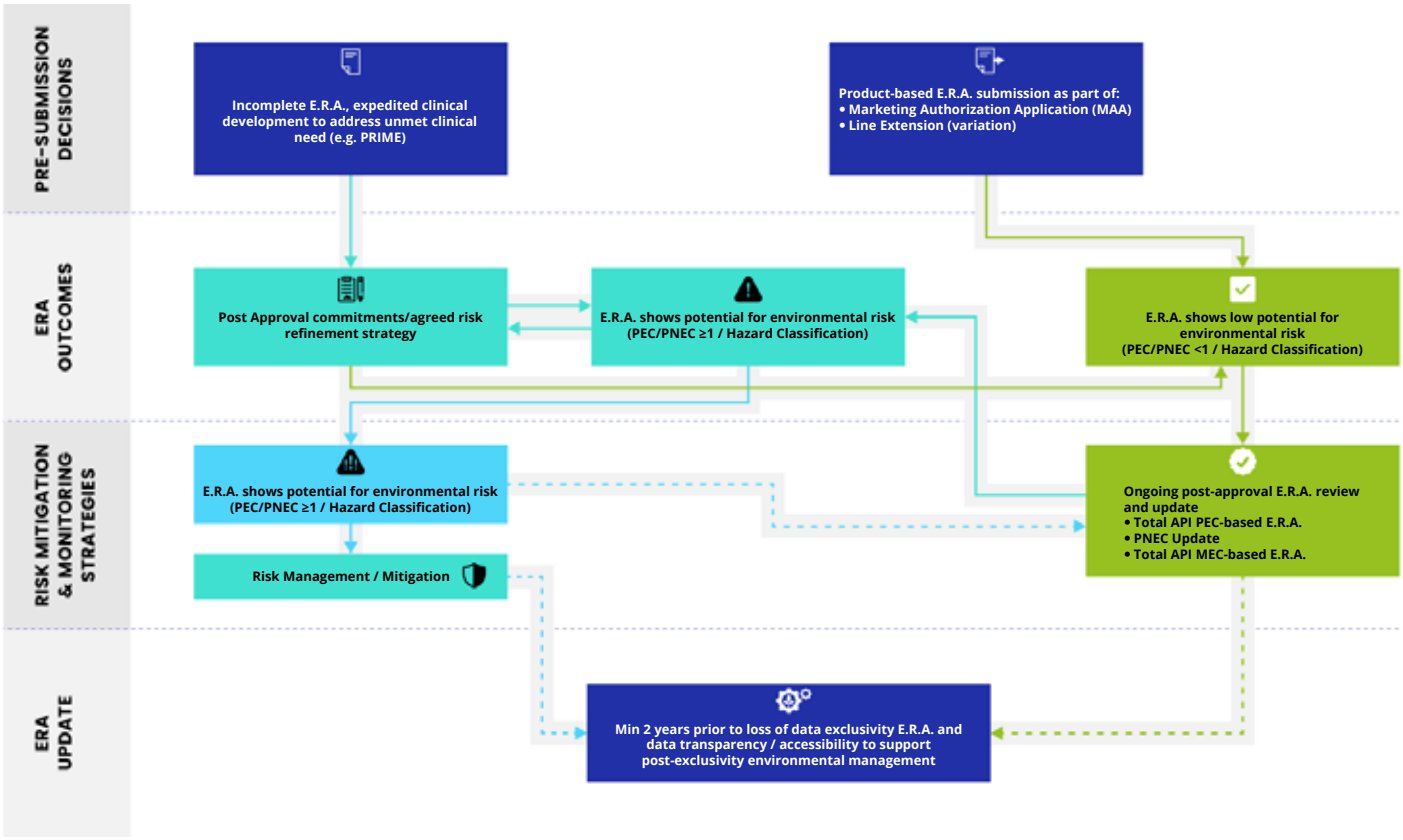
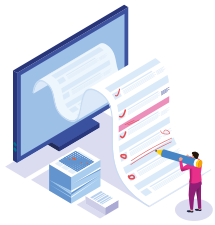



**Figure 2:**
Proposed eERA approach for 'Situation 1' detailing the prosed flow of assessment and management of environmental risks for innovative medicinal products



### 1. Expedited submission

For some expedited processes (e.g. priority medicines under PRIME where there are unmet clinical needs) or when a medicinal product is in-licenced late in clinical development, it may be difficult to produce full environmental datasets in due time for a MAA submission. However, it is critical that the generation and assessment of environmental data does not restrict or delay patient access to MPs. Under such circumstances it is suggested that binding timelines should be agreed between the applicant and the health/environmental authorities for agreed data and E.R.A.s to be provided as mandated post-approval commitments. Details of the data to be generated as post-approval and the agreed timelines should be detailed in the EPAR or via another appropriate mechanism. It is the responsibility of MAHs to ensure post-approval commitments are met according to such agreements and within the agreed timeframes. Subsequently, once an E.R.A. has been submitted and approved (updated EPAR is published), the general eERA process for expedited or standard submissions and the need for any risk refinement applies.

### 2. Standard submissions

For submissions where it is feasible to generate data and E.R.A.s along normal submission timelines, it is the responsibility of the applicant to submit an E.R.A. as part of a MAA or any relevant variations. The applicant is responsible for ensuring that the relevant guidelines are followed:

## Pre-submission meetings & EU authority alignment

Any necessary pre-submission meetings, discussions and decisions for submissions should be undertaken with the relevant regulatory bodies, taking into account the regulatory procedure being followed. It is recommended that there should be resources available at health/environmental authorities for pre-submission clarifications where there is potential for ambiguity (e.g., around triggers for certain data generation, the need for a tailored E.R.A., or active substance specific risk assessment activities). Appropriate procedures should be established to ensure alignment across EU authorities to ensure that the best environmental data and assessments are submitted by applicants. The need for a pre-submission meeting is not limited to Situation 1 of eERA, they may also be necessary under Situation 2 and 3 to agree testing plans, tailored E.R.A.s etc.

## Environmental Risk Assessment Outcomes

Currently, it is the MAHs responsibility to ensure the E.R.A. is submitted in a timely manner and according to all relevant guidelines and commitments. Once submitted if the E.R.A. PEC/PNEC ratio (RQ) is <1 for all environmental compartments then the environmental risk is considered to be low or insignificant. The MAH of the innovative product is required to update the E.R.A. where a new variation application requires such (e.g., new indications, increasing prevalence, increasing the use of the API, leading to an increase in environmental exposure) or where new data is available which affects the risk conclusions (see risk mitigation and monitoring strategies section).

Under the eERA approach there would be a new responsibility of the innovator MAH to ensure that an updated E.R.A. is generated prior to the loss of data exclusivity (e.g., 2 years) utilizing all relevant and reliable environmental data at the time and that this update is made transparent through an approach developed and agreed with the regulatory authorities in the EU that forms part of the terms of reference of the E.R.A. Expert Group and the updated EMA E.R.A. guideline.

It is beyond the scope of this document to extensively discuss risk assessment strategies, guidance or refinement approaches as this will be largely API-specific.

Where the resulting RQ of the E.R.A. is ≥1 (indicating potential environmental risk of the API) or hazard classification suggest concern (e.g. PBT) there are a number of options open to MAHs and regulatory bodies:

- Risk refinement where open literature or other additional data is available (e.g. refining disease prevalence data or use of consumption data)
- Post-approval commitments to refine the risk using further data yet to be generated (e.g. additional species testing or biodegradation data)
- Move directly to risk mitigations measures to be agreed with the relevant regulatory authority.

## Risk Mitigation and Monitoring Strategies

For post-approval mitigation and monitoring strategies there are two key scenarios to consider: (1) where the RQ ≥1 or hazard classifications suggest an environmental concern and (2) where there is no indicative hazard or risk suggested from the E.R.A.. The eERA approach advocates ongoing activities as relevant in both of these scenarios to ensure the longevity and relevance of E.R.A.s as well as proactively monitoring and managing the risk of innovative APIs that pose a potential environmental risk.

### 1. E.R.A. suggests concern (e.g. RQ ≥1 or hazard classification)

Where the E.R.A. conducted to the EMA E.R.A. guidance at the time of a MA has indicated a potential concern, and risk refinement and data generation options have either been exhausted or are not appropriate, then the eERA approach advocates risk mitigation and management. It is beyond the scope of this document to suggest appropriate risk mitigation measures as these will be dependent on the risks identified, their magnitude, and the nature and use of the API or medicinal product being assessed. Historically mitigation measures have included labelling requirements to advise clinicians and patients on appropriate disposal and inclusion of certain APIs on EU-wide, or national and regional monitoring lists (e.g. Water Framework Directive).

It should be recognised that in many instances the risks highlighted by an E.R.A. for a newly developed API will be based on highly conservative assumptions and that prior to commercialisation of a medicinal product many data are lacking such that refinement may not be possible (e.g., accurate market penetration data). It should also be recognised that risks are extremely unlikely to be manifest in the immediate period after the marketing authorisation approval, so opportunities exist to assess whether risks are being manifest in reality after MPs become established in the market.

Monitoring the scientific literature and periodic updates to the E.R.A. will also help support risk management to understand environmental risks, especially for APIs where environmental monitoring data is being generated. The eERA approach advocates such an approach and this will help provide confidence in understanding the inherent conservatism in regulatory E.R.A.s for APIs which show medium to low environmental risk.

### 2. E.R.A. suggests low potential for concern (e.g. RQ<1 or no hazard classification)

For products which show a low or insignificant risk via a standard or refined E.R.A., it remains important to continue to review the data behind such assessments and the assumptions made at the point of authorisation as this can be driven by changes to the approved use or through new data availability for the API. This regular review and updating of E.R.A.s has been termed Ecopharmacovigilance (EPV) by some authors (e.g. Velo, 2007[19]; Holm et al., 2013[20]; Wang et al., 2018[21]), ecopharmacology (Kummerer and Velo, 2006[22]) and environmental pharmacology (Rahman and Khan, 2006).

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[19] Velo, G 2007 Why Ecopharmacovigilance? Drug Safety 30(10):919-990 https://www.researchgate.net/publication/239967278_Why_Ecopharmacovigilance

[20] Holm, G., Snape, J. R., Murray-Smith, R., Talbot, J., Taylor, D., and Sörme, P. 2013. Implementing Ecopharmacovigilance in Practice: Challenges and Potential Opportunities. *Drug Saf.* 36 (7), 533–546. doi:10.1007/s40264-013-0049-3

[21] Wang et al. 2018 Adapting and applying common methods used in pharmacovigilance to the environment: A possible starting point for the implementation of eco-pharmacovigilance. Environmental Toxicology and Pharmacology 61 DOI:10.1016/j.etap.2018.05.020

[22] Kümmerer & Velo 2006 Ecopharmacology: A New Topic of Importance in Pharmacovigilance. Drug Safety volume 29, pages371–373

There are three key aspects which the eERA approach advocates that MAHs proactively engage with after approval: (i) ensuring any new products which contain the same API are collated to form an overall total API based E.R.A.; (ii) that new reliable and relevant fate and effects data which could affect the E.R.A. are updated where reliable and relevant; and, (iii) that Measured Environmental Concentration (MEC) and consumption data (where available) are considered in the E.R.A.. Each of these aspects will be examined in detail below:

### (i) Total API PEC

Current E.R.A.s are required to be product specific and be updated with all indications for which that product is used. This requires E.R.A.s to be updated and the impact on the environment evaluated when variations may cause an increase in environmental exposure (European Medicines Agency, 2006[6]). Whilst this is not considered inappropriate this approach fails to account for the overall environmental load of that API in the environment. The eERA approach proposes that the originator MAH includes the contribution from all MPs containing the assessed API. This total PEC-based API approach therefore includes all indications for all MPs which may contribute to the environmental concentrations of the API in the EU. This approach is aligned to some extent to that used US Food and Drug Administration (FDA 1998[23]) where total API sales forecasts are used rather than product specific information.

### (ii) New fate and effects data

As well as updates to the E.R.A. as a result of potential environmental exposure increases associated with multiple indications for a given API, the eERA approach extends these updates to also include new data which is published in the peer reviewed scientific literature where reliable and relevant. The incorporation of peer reviewed data should be included when updating the E.R.A. with new variations. Use of this type of data in regulatory assessments has been suggested by many authors and was included also in the recent draft update to the EMA's E.R.A. guideline (European Medicines Agency 2018[24]). It is critically important to ensure that data are assessed for reliability and relevance prior to any incorporation of such data in E.R.A.s (e.g. Klimisch et al 1997[25], Moermond et al 2016[26]).

It is recommended that as well as calling for incorporation of peer reviewed data regulatory authorities should also provide guidance and criteria on relevance and reliability to improve consistency during technical review and decision-making by the relevant authorities. Reliability and relevance criteria are described in the literature (e.g. Klimisch et al 1997[25], Moermond et al 2016[26]) and are frequently used in many fields of environmental assessments. Where new data are published that may significantly influence the risk conclusions the E.R.A. expert group may reach out to appropriate MAHs to seek clarification.

### (iii) Use of Measured Environmental Concentrations (MECs) and consumption data

Once MPs are on the market MECs and consumption data, where they exist, should be collated from the open literature and available monitoring programmes to add realism and address uncertainty in the PEC-based E.R.A.. Consumption data can be used directly in the calculation of PECs to provide some realism to unrefined exposure calculations, or utilised in more advanced exposure models, such as ePiE used to look at spatially explicit environmental exposure and risk, for comparison to MECs (Oldenkamp et al., 2018[25]). It should be noted that MECs only represent a single point in time and are location specific; therefore, MECs are often not suitable for direct use in the E.R.A.. However, MEC data can be utilised to create semi-probabilistic risk assessments, such approaches have been discussed in previous peer reviewed publications (e.g. Holm et al., 2013[20]), and there are multiple techniques to utilise such measured data in the overall evaluation of environmental risk.

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[23]Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) (1998): Guidance for Industry - Environmental Assessment of Human Drug and Biologics Applications, July 1998, CMC 6, Revision 1

[24]European Medicines Agency (EMA) (2018): Draft guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), 15 November 2018, EMEA/CHMP/SWP/4447/00 Rev. 1

[25]Klimisch et al 1997 A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regulatory Toxicology and Pharmacology. Volume 25, Issue 1, Pages 1-5 https://doi.org/10.1006/rtph.1996.1076

[26]Moermond, C.T.A., R. Kase, M. Korkaric & M. Agerstrand. 2016. CRED: Criteria for reporting and evaluating ecotoxicity data. Environmental Toxicology and Chemistry 35(5): 1297-1309.

## E.R.A. Update

Finally, under the eERA model, it is the responsibility of the MAH to update the E.R.A. using all relevant and reliable data 2 years prior to the loss of exclusivity; this timing will support ongoing environmental risk management while the MAAs of generic companies are under preparation and evaluation by the EMA and / or National Competent Authorities. As discussed above, such data should include consumption-based PECs accounting for all registered uses of the API in the EU, new reliable and relevant effects data and also any relevant MEC data available. This ensures that prior to the entry on the market of any off-patent API based medicinal products the best estimate of environmental risk is available including margins of safety.

These E.R.A.s, as well as the supporting environment fate and effects data, should be made transparent and accessible to the whole pharmaceutical industry as well as the wider scientific community and general public.

Such transparency will:

- Provide the foundation to manage environmental risks across the MP lifecycle, including Situations 2 and 3 described below
- Improve credibility and visibility in the scientific rigor of the regulatory processes
- Reduce unnecessary duplication of testing (namely vertebrate testing) by future applicants / innovators and academia
- Increase regulatory consistency in the environmental assessment process and decision-making including E.R.A. refinement approaches across different Member States
- Allow regulatory conclusions to be consistently applied across all MPs
- Improve consistency and harmonisation in labelling language across different MPs containing the same APIs and therefore carrying the same inherent environmental risks
- Allow for a more realistic total PEC to be generated through the incorporation of total consumption and MEC data rather than limiting assessments to MP specific indications.

# SITUATION 2: Off-patent APIs

**Situation 2 describes the need for automatic-reference to E.R.A. and associated data of the reference product dossier in two cases: off patent API and new indication for an existing API (see Figure 3).**

### 2.1. Off-patent generic APIs

Where the off-patent medicinal product is intended as an alternative equivalent therapeutic option for the reference medicinal product on the market, the modalities of clinical use will remain similar. Off-patent MPs, since they contain an equivalent version of the API available in the reference product, are generally considered not to influence the overall environmental risk associated with the API unless there is a significant increase in environmental exposure.

The proposal carried over via the revised draft E.R.A. guidance, suggests use of a Letter of Access approach to the environmental data. Such approaches have proven to be not fit-for-purpose, leading to the request to repeat studies, since data sharing is in reality very challenging. In turn this can lead to alternative and conflicting E.R.A.s being produced by multiple MAHs for the same API. Duplicate testing and generation of alternative risk assessments leads to an unnecessary utilisation of resources in the contract laboratories and an increased risk of generation of conflicting E.R.A. conclusions for the same API, whilst doing little to improve environmental protection. The option to make an automatic reference to these E.R.A. and supporting studies will also minimise the administrative burden on the new applicants and on the responsible Authorities responsible for the evaluation of MAs.

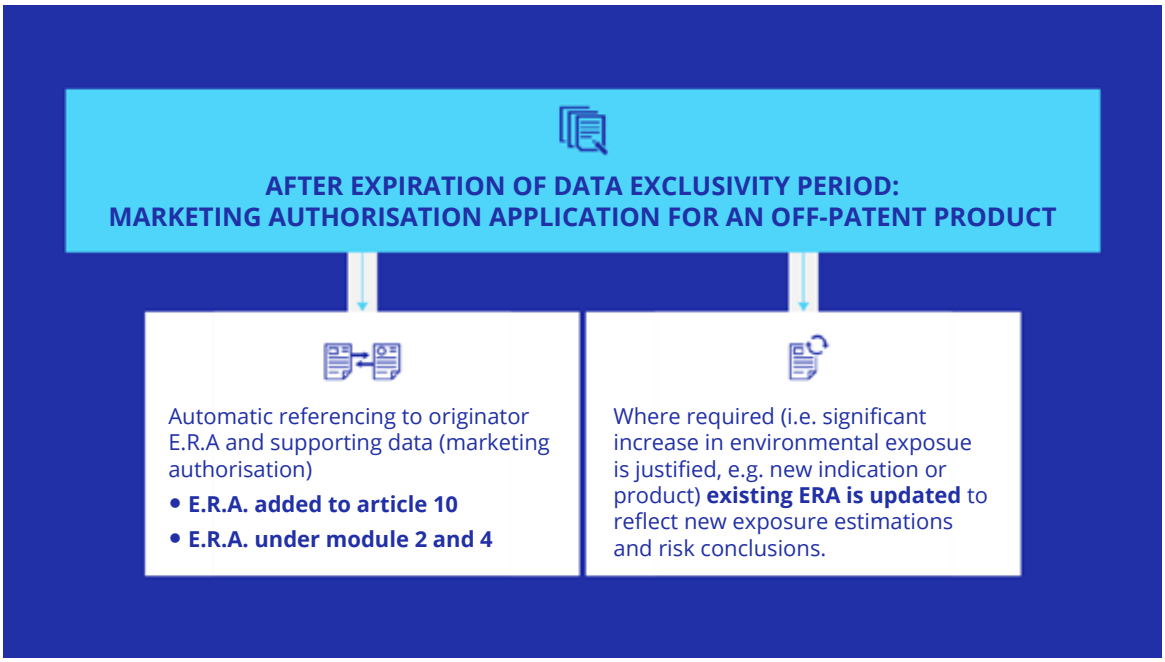



**Figure 3:**
Proposed eERA approach for 'Situation 2' detailing the proposed role of automatic-referencing existing E.R.A.s and when further updates would be required. Details of the situations in which updated E.R.A. is required and drivers of increase in environmental exposure are given in the text below

A medicinal product authorised under article 10 of the Directive 2001/83, is allowed to refer to the reference product data by demonstrating essential similarity with the reference product, thus confirming equal efficacy as well as safety for the user and the environment, under similar clinical use conditions.

The E.R.A. and associated environmental data are safety studies and therefore it can be included in the exemption provided in article 10 of the Directive 2001/83[27] according to which the applicant shall not be required to provide own study results of pre-clinical tests and of clinical trials, if one can demonstrate that the medicinal product is a generic, hybrid, well-established use or biosimilar of a reference medicinal product which is or has been authorised under Article 6, for not less than eight years in a Member State or in the Community, to be used in similar clinical conditions. Just like other safety studies in the regulatory dossier, it should be allowed to all new marketing authorisation applicants to automatically refer to the environmental data and the E.R.A. of the reference product.

The current location of the E.R.A. in Module 1 (Administrative Information and Prescribing Information) of the regulatory dossier is inappropriate, and a relocation of such performed studies to "other scientific data" section within Module 4 and consequently in module 2, is required. Automatic-referencing to the reference product environmental data under Module 4 as "other study" (Module 4.2.3.7.7) will allow the off-patent applicant to reference to the already assessed E.R.A. for the same API. In this way the regulatory workload also remains unchanged, compared to the case, where off-patent sector would have to perform own studies, thus repetition of the workload for the regulators is multiplied in line with numbers of the off-patent MAs.

**Benefits of automatic-referencing for off-patent APIs**

Since the pharmaceutical legislation is open for review, this is the opportunity to create a fit-for-purpose framework by including E.R.A.-related studies with the rest of the toxicology studies.

The proposed solution of referencing to already approved E.R.A.s provided in the reference product dossier will avoid repetition of studies. The automatic-reference to E.R.A. data that was already generated, validated & evaluated for the reference products, will optimise the process. There will be neither the need to ask the MAH of the reference product to share data and studies, request letters of access which come with a huge administrative and logistical burden, nor will there be the need for repetitive evaluation of such E.R.A. data by the regulatory authorities. It would also focus E.R.A.s at the point of generic market entry on APIs that have lowest margins of safety and potentially the highest risk, rather than all APIs.

## 2.2. New indications or combination products for off-patent APIs

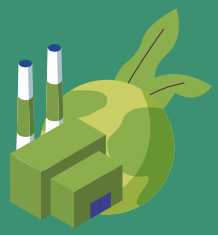
When, for example, a new indication or combination product for existing APIs is submitted, there is potential that the risk increases for that API, through increased market penetration and environmental exposure. The applicant needs to be able to refer to the previous E.R.A. available via the final stage of situation 1, update these E.R.A. assumptions and demonstrate that the new indication does not increase that RQ > 1. It may also be appropriate to consider allowance for justification for not providing full E.R.A.s for APIs which have a margin of safety >10 (i.e. where RQ < 0.1). Where high margins of safety have been well established (e.g. >10x) through the processes outlined in situation 1, it is highly unlikely that new MPs or indications will erode this margin of safety and pose a risk.

Contrary to the originator applicant, new MA applicants currently don't have access to the environmental data supporting the existing E.R.A.. Therefore, this further demonstrates the need for a mechanism to either increase the transparency of E.R.A.s and their supporting data, or get confirmation from an EU centralized body, whether there is a need for any E.R.A. revision due to the potential increase in the consumption of the API due to new indication(s) or MPs. In the situation that there is an increased risk, the need for exposure re-assessment and the refinement of the E.R.A. may indeed be needed. It may also be appropriate to consider examination of the peer reviewed literature, particularly where margins of safety are large.

[27]Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

# SITUATION 3: Environmental risks associated with legacy APIs

**Situation 3 within the proposed eERA framework involves the assessment and management of the environmental risk of so-called 'legacy' APIs, that is those APIs approved prior to the E.R.A. guidance being adopted in (2006 CPMP/SWP/4447/00, 2006).**



**There are a large number of 'legacy' APIs (likely to be in region of 1000 APIs) with incomplete data to adequately conclude on environmental risk. Therefore, the generation of such data needs to be prioritised to avoid unnecessary pressure on limited environmental testing capacity in contract research organizations (CROs), that might compromise testing availability associated with the delivery of innovative products from the pharmaceutical and wider chemical industry.**

It has been demonstrated by several studies (e.g. Burns et al 2018[28]; Gunnarsson et al 2019[15]) that few APIs that have been tested to date pose a potential risk to the environment. There are often key properties for those APIs of concern which can help to identify and prioritise them (e.g. endocrine active mode of action and high lipophilicity) and many of these properties are already recognised in the current E.R.A. guideline[1]. It is also important to consider the value that alternative and intelligent testing strategies such as the use of predictive, *in silico* and *in vitro* tools will play in reducing or avoiding unnecessary and particularly animal intensive testing. The prioritisation of testing of legacy APIs and development of intelligent testing methods has been, and continues to be, a significant research priority for the pharmaceutical industry and the European Commission through the IMI.

The outcomes of the IMI iPiE[9] – Intelligence-led Assessment of Pharmaceuticals in the Environment project (2015-2019) – enabled consortia members to develop a prioritisation framework to help identify those APIs that are most likely to present a risk for the environment (Burns et al 2018[28]). This multi-stakeholder project created a publicly accessible database on environmental information including more than 2000 studies for approximately 200 legacy APIs. Spatially explicit environmental exposure and risk modelling tools (e.g. e-PIE, the 'e' stands for exposure; Oldenkamp et al 2018[29]) and a comparative genomic tool-box to search across taxa for drug target conservation (e.g. EcoDrug, Verbruggen et al 2019[30]) were also developed under iPiE. Other science-based tools to identify the environmental risks that MPs pose are equally available, examples include gill and liver cell assays to assess toxicity, uptake and metabolism of APIs in fish (OECD, 2021)[31].

[28]Burns EE, Carter LJ, Snape J, Thomas-Oates J, Boxall ABA. 2018. Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. J Toxicol Environ Health B Crit Rev 21: 115– 141.

[29]Oldenkamp et al 2018 A High-Resolution Spatial Model to Predict Exposure to Pharmaceuticals in European Surface Waters: ePiE - PubMed (nih.gov)

[30]Verbruggen et al 2019 ECOdrug: a database connecting drugs and conservation of their targets across species | Nucleic Acids Research | Oxford Academic (oup.com)

[31]OECD, 2021 Test No. 249: Fish Cell Line Acute Toxicity - The RTgill-W1 cell line assay

Based on the iPiE database and data in publicly available EPARs and Fass.se, Gunnarsson et al., 2019[15] conducted E.R.A.s for over 120 APIs, using full EMA environmental datasets and worst-case country specific consumption data. These indicated potential risks (i.e., PEC/PNEC ratios ≥1) were limited to less than 5% of APIs and a few mechanisms of action.

To further improve environmental data and also our capability to prioritise, predict and assess potential environmental risk of 'legacy' APIs, innovative research continues under the current IMI PREMIER[10] (Prioritisation and Risk Evaluation of Medicines In the Environment) project.

This project includes stakeholders from academia, industry and regulatory authorities and is referenced as a flagship initiative within the EU Commission's Pharmaceutical Strategy for Europe 2020.

The project was initiated during 2020 and runs until 2026. The aim is to improve models that can predict the environmental exposure and the environmental effects of APIs. The outputs may also be applied to screen new APIs to advance drug candidates for development that are less likely to be problematic from use and disposal, and to target environmental testing needs as outlined by Burns et al., 2018[28]. PREMIER will also increase the transparency and accessibility of environmental risk assessment data to all stakeholders through a publicly available digital assessment system.

## Prioritisation

Both the iPiE project and the current PREMIER projects have a significant focus on prioritising the testing of legacy APIs. Building on the work of iPiE, the PREMIER project is focusing on the development of a decision framework for prioritisation of APIs with incomplete environmental datasets. Prioritisation of APIs within PREMIER will focus on tools that screen for both environmental hazard and risk potential.

These tools are currently being applied to prioritize APIs of high potential concern to allow target testing. Hazard criteria focus on groups of molecules with common mechanisms of action which are currently under-represented from a data perspective and lack environmental toxicity studies (i.e. APIs where limited or no ecotoxicity data exists). Criteria to further prioritise case study APIs within these groups include consumption or use data in EU, chemical structural similarities and read across, bioaccumulation potential (log $K_{OW}$), water solubility and potency. Risk criteria focus on filling data gaps of potentially high-risk APIs.

Prioritisation of case study APIs through both hazard- and risk-based approaches will result in the generation of environmental fate and behaviour, ecotoxicology and/or environmental concentration data. This data generation aims to demonstrate the utility of the various factors considered in effective prioritisation schemes, enabling such schemes to be further considered in future legislative and regulatory frameworks.

Whilst the PREMIER research project is focusing individually on both hazard and risk as prioritisation tools, there is some degree of overlap between the two. In reality, any prioritisation scheme promoted for practical use will utilise a combination of factors, both hazard and risk based, in order to effectively manage the burden of testing required for legacy APIs.

It is also important to note that prioritisation of testing may result in the generation of data for specific APIs only to conclude on their environmental risk rather than a full E.R.A. dataset i.e. focus testing on particular environmental fate studies or particular species/ endpoints that are the most important. Additionally, there are other higher throughput or more focused investigative tools being developed within PREMIER which may be used to understand the critical aspects of the data for APIs that have lower concern.

## Intelligent Testing and Assessment

One of the aims of PREMIER is to deliver an API information and digital assessment system (DAS) for characterising the potential environmental risks of APIs, including relevant human metabolites and environmental transformation products, based on optimised testing. This system will be designed to enable screening and prioritisation of legacy APIs for a tailored environmental assessment; to identify potential environmental hazards associated with APIs in development; and to make the available environmental data transparent and accessible for all stakeholders.

The basis for this initiative on intelligent testing builds on the work delivered through the preceding iPiE project that developed a suite of data, tools and models to help researchers assess which APIs are most likely to get into the environment, and which APIs could be harmful to wildlife and ecosystems.

New models to predict levels and activity of APIs in the environment were also developed. For example, iPiE created the ePiE tool (Oldenkamp et al., 2018[29]), which models the path of an API from the moment it is taken by a patient, via the toilet and sewage pipes to waste water treatment plants, to the moment it is released into a river. The tool draws on national consumption data of different APIs and their chemical properties and delivers a prediction of the concentration that would be found in certain key European river basins on a spatial scale.

iPiE has also created computer algorithms called QSPRs (quantitative structure property relationships), which analyse the chemical properties of APIs to predict what will happen to them and how they will behave in the environment, e.g. whether they are likely to break down in a wastewater treatment plant, or adsorb to soil particles.

Another key question in environmental risk assessment is knowing which APIs are most likely to cause harm to wildlife. After all, APIs are designed to be biologically active, and although millions of years of evolution separate us from fish, for example, we do still share a number of proteins in common. This means that if a freshwater fish has a protein that is also a target of an API, it is likely that the API could target fish if it is released into surface waters. To help scientists quickly find out which API targets are also found in wildlife, iPiE created the ECOdrug database[32]. The publicly available tool draws on data from multiple sources and has information on over 600 species, including other primates, rodents, birds, fish, microscopic animals, fungi, and plants.

The PREMIER project intends to increase the knowledge and applicability of such intelligent exposure and effects models by:

- Developing predictive methods for characterising the environmental fate properties and exposure concentrations of APIs in surface waters, sediments, soil and wildlife food items to support prioritisation, and tailored testing, of APIs under Situation 3.
- Testing up to 25 APIs where incomplete E.R.A. data exist to help validate and build stakeholder confidence in the prioritisation approach and associated tools to increase the data and knowledge-base for classes of APIs that lack environmental data.
- Developing and refining a complementary series of *in silico* models for predicting API effects to help screen candidate APIs in drug development (Situation 1) and reduce vertebrate testing for legacy APIs (Situation 3). *In silico* models include drug (on and off) target orthologue prediction and chemical read-across.
- Developing and refining a complementary series of *in vitro* assays for predicting the uptake, metabolism and effects of APIs in fish to reduce vertebrate testing of legacy APIs (effects and bioconcentration-based studies in Situation 3). Fish show high levels of human drug target conservation and are likely to be amongst the most impacted organisms by environmental exposures to APIs.
- Predicting pharmacological and harmful effects of APIs in non-target organisms and to assist with the iterative assessment of APIs and targeted testing in Situations 1 and 3. This will be achieved through the development and application of novel approaches for combining drug pharmacokinetics with effect measures and taxonomic read-across between humans and other vertebrate models (i.e. fish, amphibians, reptiles, birds and mammals).

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[32] https://i-pie.org/ipie-ecodrug/

### Transparency and data accessibility

The IMI project PREMIER will establish a database and digital assessment system (DAS) on environmental data of various APIs. The studies included are reported in detail and the DAS will be publicly accessible at no charge. The public data access ensures full transparency on the environmental data and can be used as a tool to avoid multiple testing of APIs. Moreover, the DAS will include in silico tools/models which allow scientists to close data gaps. Also, it can be used for prioritization and identification of those APIs which are likely to cause a risk in the environment.

PREMIER will agree on the structure and content of the PREMIER E.R.A. database and will populate it with existing GLP and (E)PAR data for APIs on the EU market that underpin the E.R.A. process. Non-standard environmental toxicity data will also be included for prioritised APIs where it has been deemed to be both reliable and relevant according to CRED (Moermond et al., 2016[26]).

The digital assessment system (DAS) will be developed such that it meets the needs of key stakeholders responsible for managing the potential risks posed by pharmaceuticals in the environment across their life cycle. The DAS will be a web-based system that allows stakeholders to interact with the main project outputs.

The DAS will (i) support the prioritisation and evaluation of legacy APIs with regard to their potential environmental risk, (ii) enable spatially explicit environmental exposure assessments to be conducted across EU river basins, (iii) facilitate the dissemination and accessibility of relevant and reliable environmental fate and effect data to interested stakeholder groups in a consistent manner, (iv) provide tools to conduct the ecopharmacovigilance of authorised APIs through the integration of environmental data published post-authorisation and measured environmental concentrations of APIs such that semi-probabilistic E.R.A.s of specific APIs can be conducted to look at 'real-world' and 'real-time' environmental risks resulting from patient use.

## IMPLEMENTING eERA

Whilst an extended E.R.A. approach as described above represents a significant step forward, there are a number of topics that need to be considered and addressed. These include:

- Regulatory and other stakeholder engagement buy-in, co-ownership and agreement on the final eERA mechanism that meets the needs of all regulatory and industry stakeholders
- An E.R.A. expert group for regulatory oversight is required for human medicinal products that captures centralised, decentralised, mutual recognition and national marketing applications to proactively manage environmental risk (including E.R.A. updates) throughout the MP and API life cycle
- An appropriate mechanism needs to be established to increase transparency of E.R.A. data in a consistent and searchable format (IMI Premier project will deliver a potential solution subject to approval and adoption by wider stakeholder community)
- The ability to automatically-reference environmental data that has been subject to evaluation by national competent / relevant authorities thus preventing duplication of testing and mitigating conflicting E.R.A. interpretations
- Managing environmental risks based on total API use

## OVERSIGHT AND COORDINATION

The review of the data submitted in the three situations described above require regulatory oversight and a decision-making body. This is most apparent when there are:

- mode of action specific concerns to be addressed via a tailored E.R.A.,
- environmental risks that need to be refined through post-approval commitments,
- inconsistent results from studies that underpin an E.R.A. identified from the literature that require resolution,
- issues which arise when a total API-based approach is applied, highlighting issues that need to be addressed by multiple MAHs across multiple MPs,
- differences in opinions that need to be resolved between Member States or between Member States and industry

In line with the EU Strategic Approach to Pharmaceuticals in the Environment (COM(2019)128)[14], where under section 5.3 a requirement for "Improvement of the E.R.A. and its review" is listed, we suggest establishing a body of environmental risk assessors from relevant competent authorities to perform this data evaluation in the framework of eERA. Such a body could be responsible for:

- Providing recommendations to relevant authorities responsible for issues regarding medicinal products for human use on any questions relating to E.R.A. activities with respect to medicinal products for human use and on environmental risk management options, including ensuring the effectiveness of those management options.
- Developing and updating science-focused environmental guidance based on risk
- Engaging with MAHs to address E.R.A. concerns and action plans, including the design and evaluation of post-authorisation studies, where there are risks identified:
  - During evaluation of the MAA so they can be addressed post-approval
  - Through the ongoing environmental stewardship of authorised MPs
- Coordinating the environmental safety issues at the MP and API level
- Agreeing on a single environmental effect assessment (PNEC) for each environmental compartment per API where multiple data exist
- Working with industry to coordinate the tailored E.R.A. for legacy products by agreeing on the priority APIs for testing and the minimum data required to conclude on risk to maximise coverage of APIs

The composition of this environmental regulatory body, its accountabilities and reporting line needs to be established in a dialogue between all involved stakeholders. It should be noted that this process needs to cover all types of marketing authorization procedures in the EU, i.e. centralized, decentralized, mutual recognition and national, in order to obtain results applicable in all Member States. Potential roles and responsibilities for industry and regulatory stakeholders are captured in the table below.

| Marketing Authorization Holders (ERA data owner) Roles | Regulatory (relevant Authority) Roles |
|---|---|
| • Update the E.R.A. if required<br>• Innovator MAHs update the E.R.A. prior to the loss of exclusivity | Ownership and oversight of the eERA process |
| Establish internal processes for E.R.A. updates and implement consistent procedures | Establish responsibilities and capacities for communication with MAHs on post-approval commitments |
| Agree to a formal reporting process and timings with regulators | Engage in risk refinement and risk mitigation discussions with industry and other stakeholders |
| Support all efforts to increase the transparency and consistent reporting of environmental risk data | Establish publicly accessible database for environmental EPARs/ E.R.A.s at MP and API level |
| Proactive engagement off all MAHs and establish cost-sharing models need to be developed where new environmental data are required | Provision that all new marketing authorisation applications can use existing E.R.A. data from reference marketing authorisations through automatic-referencing, e.g. via an update of articles 10(1), 10(3), 10(4), 10a, 10b, 10c of Directive 2001/83/EC (06. Nov. 2001 as amended). |

## SUMMARY AND CONCLUSIONS

The currently used E.R.A. methodology in the EU is a MP-based assessment which considers the risk of a specific API under the specific indications and uses of the MP under assessment. The E.R.A. data (unlike preclinical and clinical data) is currently not permitted to be automatically-referenced without a formal letter of access granted by the MAH of the reference MP. There is a requirement for multiple MAHs marketing the same API to present their own E.R.A. data in their respective MAAs which can drive duplication of studies. Not all industry data is available publicly and the data that has been publicly presented in EPARs as well as in PARs also lacks consistency, detail, and transparency. The current E.R.A. methodology limits the utility of the published E.R.A.s for understanding the risks of APIs which are used in multiple MPs. Also, the lack of consistency and transparency of the publicly accessible study detail makes the understanding of which MAHs own which data difficult.

In summary, this can lead to duplication of studies (posing bioethical concerns), inconsistent and conflicting E.R.A. conclusions and non-equitable testing burdens on individual companies. The eERA framework provides numerous benefits including:

- Industry's continuous commitment to conduct robust and risk-based E.R.A. without compromising environmental protection or patient access to medicines
- The need for risk identification, refinement and management during the MAA evaluation process with appropriate follow-up responsibilities defined
  - no need for independent and duplicative risk identification and prioritisation processes under additional legislation (e.g. Water Framework Directive) in addition to the pharmaceutical legislation in the broadest sense
- A focus on risk that reduces the burden on regulatory oversight and industry as most APIs (>90%) indicate low or insignificant risk
- Avoiding duplication of testing provides bioethical benefits
- Updating E.R.A. across the API and MP life cycle as needed; thus ensuring that the E.R.A. reflects the latest environmental information
- Increasing the transparency of, and access to, E.R.A. data with the ability to automatically-reference E.R.A. data in MAAs

The pharmaceutical industry is committed to working with all stakeholders to establish the eERA approach as working practice, help promote transparency and improve environmental protection within the European Union.

# ABBREVIATIONS

| | |
|---|---|
| **AESGP** | Association of the European Self-Care Industry |
| **API** | Active Pharmaceutical Ingredient |
| **CHMP** | Committee for Medicinal Products for Human Use |
| **CMDh** | CMDh: Coordination Group for Mutual Recognition and Decentralised Procedures - Human |
| **DAS** | digital assessment system |
| **EFPIA** | European Federation of Pharmaceutical Industries and Associations |
| **EMA** | European Medicine Agency |
| **EPAR** | European Public Assessment Reports |
| **EPV** | Ecopharmacovigilance |
| **E.R.A.** | Environmental risk assessment |
| **eERA** | extended Environmental Risk Assessment |
| **EU** | European Union |
| **GLP** | Good Laboratory Practice |
| **IMI** | Innovative Medicines Initiative |
| **iPiE** | Intelligence-led Assessment of Pharmaceuticals in the Environment project |
| **MA** | Marketing authorisation |
| **MAA** | Marketing authorisation application |
| **MAH** | Market Authorization Holders |
| **MECs** | Measured environmental concentrations |
| **MPs** | medicinal products |
| **PARs** | Public Assessment Reports |
| **PiE** | Pharmaceuticals in the environment |
| **PNEC** | Predicted No Effect Concentrations |
| **PREMIER** | Prioritisation and Risk Evaluation of Medicines In the Environment project |
| **QSPR** | quantitative structure property |


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