BLUE FROG SCIENTIFIC

SETAC EU 2026 - Presentation ID: 3.21.P-Tu372

Environmental Risk Assessment of Generic Human Pharmaceuticals

Authors: Martin Bowyer[1], Emilie Bigorgne-Vizade[2], Tom Hargreaves[3]
Affiliation: [1]Blue Frog Scientific Limited, Edinburgh, UK, [2]Blue Frog Scientific SAS, Lyon, France, [3]Blue Frog Scientific Limited, Swansea, UK;
Contact Us: www.bluefrogscientific.com / martin.bowyer@bluefrogscientific.com

Blue Frog are exhibiting. (Booth 79)
Come & talk with us... we'd love to hear your views!

"The outcome of the ERA should not constitute a criterion for refusal of a marketing authorisation."

In accordance with Directive 2001/83/EC, all new marketing authorisation applications must be accompanied by an evaluation of potential environmental risks posed by the medicinal product.

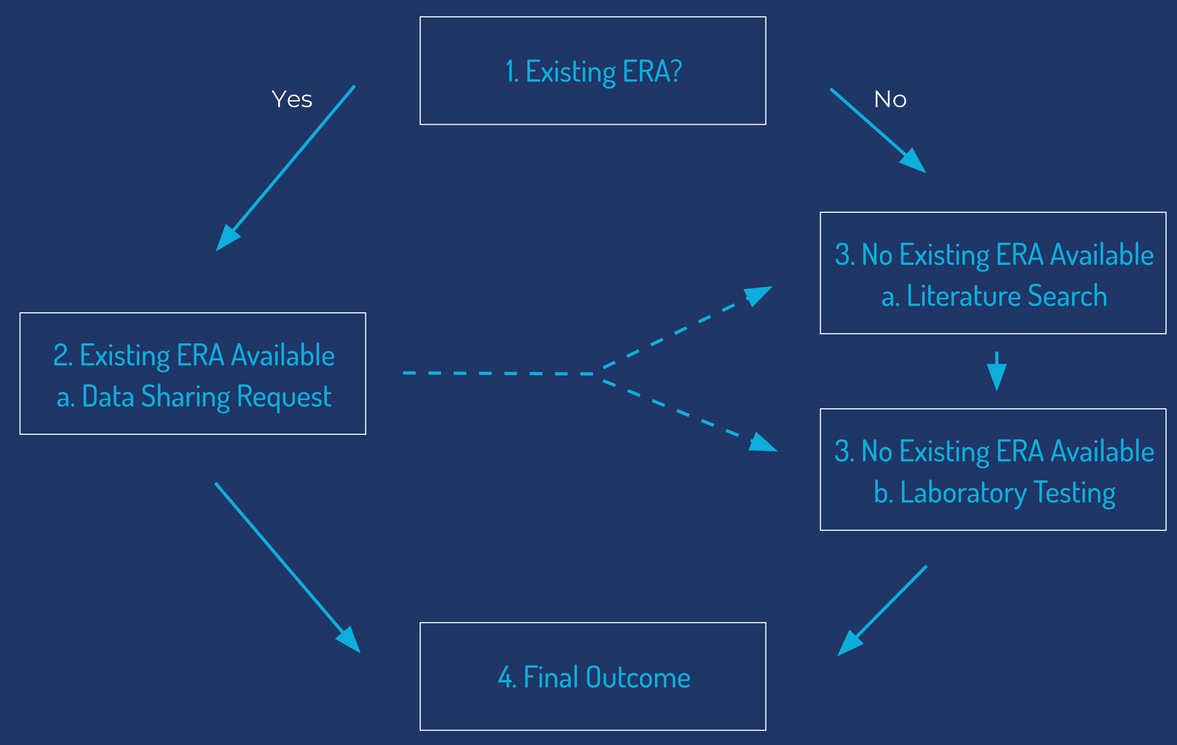
The European Medicines Agency (EMA) first officially adopted guidelines on how this should be done in 2006. These guidelines allowed, for some application and product types, for the ERA to consist only of a justification of why no risks where anticipated.

For generic products this justification was based on the assumption that no increase in environmental exposure would result from authorisation.

The Environmental Risk Assessment (ERA) does not factor into the overall approval decision of a medicinal product and the ERA is essentially a costly box ticking exercise.

In September 2024 an updated guideline came into effect. This removed the possibility for generics to rely on the previously acceptable waiver and potentially significantly increased the cost of obtaining a marketing authorisation for a generic product. This approach was adopted to ensure products that were first approved pre-2006 (i.e. have never been assessed) would be captured by the ERA guidelines and require a full risk assessment. Previously all generics of these products would simply state no increase environmental exposure and concluded no risk, despite the risk never being assessed by the originator company.

An overview of the ERA strategy for generic products, outlined in the updated EMA guidelines is presented here.



1. Existing ERA

a. Has an ERA been performed on the active substance?
- Unlikely to have been performed for any substance approved prior to 2006.
- Not always easy to confirm ERA status especially for decentralised or national procedures.

b. Does the available European Public Assessment Report (EPAR) include details and conclusions of the ERA?
- Existing EPARs for products containing the active substance reviewed to identify if an ERA is available.
- The quality and content of published EPARs varies widely. Not all information publicly available.
- Possible to confirm ERA status and conclusion by submitting an a "access to documents request" to the EMA.

c. Does the ERA remain relevant to the generic product?
- Generally an ERA for the reference product will be relevant to the generic as the indication and dose will be identical.
- However there will be deficiencies in old ERA compared to new guidelines due to updated requirements.
- Assessment of acceptability of old ERAs is highly subjective and no updates can be performed without access to the original studies.

2. Existing ERA Available

a. Request data access - Rarely if ever granted
- Data sharing is encouraged but no incentives or legal requirements exist
- Asking Marketing authorisation holders (MAH) to share data with direct competitors.
- If granted a Phase I ERA can be prepared and submitted along with the letter of access. Additional studies may be required to bring existing dataset up to compliance with the current EMA guidelines.

b. No access granted
- If data sharing cannot be agreed the guidelines state the following

"In the specific instance of generics where data sharing is not agreed, if a relevant ERA was considered satisfactory by an EU CA and the applicant is able to justify the scientific conclusions reached for the relevant ERA remain applicable to their generic product, repetition of ERA studies will generally not be required"

The EMA recently provided clarity on this text.

"EPARs or study summaries from other MAH websites are not considered sufficient to replace required studies without the underlying study data"

".....it is not possible to refer to an EPAR in lieu of submitting the actual data."

Furthermore, feedback from several generic applications indicate that without a data sharing agreement the Applicant cannot refer to any endpoints reported in the existing EPAR, rather only the EPAR conclusions can be presented, i.e. "the log Kow was <3" not the actual measured number cannot be presented.

This creates problems when any deficiencies or ambiguity is present in the existing EPAR, or updates are required. For example;
- Previous ERA used unacceptable refinement approach
- Info in EPAR not clear as to PEC or refinement methods
- Data gaps present in the original submission and EPAR not subsequently updated
- Outdated prevalence data used in assessment.

In any event where recalculation / updates to the ERA are necessary the Applicant would be required to perform all the ERA studies despite an acceptable data set being previously submitted.

3. No Existing ERA Available

a. Literature search and perform ERA based on publicly available data
- Very rarely a viable option due to lack of available data, especially concerning the OECD 209 (ASRIT), soil / sludge adsorption data and sediment toxicity
- Data gaps are very likely to exist and in-silico methods are not accepted

b. Perform new ERA studies
- Standard test package cost in region of £250,000 - £300,000 but can be significantly higher dependent on studies triggered
- Involves multiple vertebrate studies (OECD 210 and OECD 305)
- Collaboration would be highly beneficial.
  - Testing costs shared between multiple parties
  - Harmonised endpoints used in risk assessment

4. Final Outcome

ERA has very minimal impact on product and does not factor into overall risk-benefit evaluation of drug.

If risks cannot be excluded then risk mitigation measures and labelling are required. The guideline proposes the following safety measures;
- Indication of risk in SmPC
- Instructions on storage and disposal
  - The proposed disposal instructions are the same whether a risk has been identified or not

The steps required to reduce the environmental risk essential boil down to adding some additional text in the SmPC and inclusion of a standard disposal statement on the label (which is also required when no risk is identified).

Are these mitigation measures effective at reducing the environmental risk?

Conclusion

- The EMA ERA guideline update removed the previously acceptable justification for generic products to avoid submission of a full ERA.
- Existing MAH are unlikely to share data without legal requirement too.
- When data sharing is not agreed, no data reported in the EPAR can be used by the generic applicant.
  - No updates or modifications to existing ERA can be performed by new Applicant
- Significant amount of new animal studies / duplication of data will result.
- Some generic products won't be finically viable due to increased testing burden.
- Ultimate outcome of the ERA has no impact on product approval and the effect on environmental protection is questionable.

#PharmaERA #SETAC2026

www.bluefrogscientific.com/pharmaceuticals

References:
- EMEA/SWP/4447/00 Rev. 1- Corr. Guideline on the environmental risk assessment of medicinal products for human use.
- 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.