# ECO-PHARMACO-STEWARDSHIP (EPS)

## PILLAR 3 - EXTENDED ENVIRONMENTAL RISK ASSESSMENT (eERA)

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**Objective** ..... **3**

**Introduction** ..... **3**

**How eERA will work** ..... **4**

**Situation 1: New APIs prior to patent expiry** ..... **4**

**Situation 2: New APIs after patent expiry** ..... **4**

Voluntary review process ..... 5

Regulatory triggered process ..... 5

**Situation 3: Legacy APIs/medicinal products authorised prior to Dec 2006:** ..... **6**

**Key Features of a prioritised eERA review Program (Situation 2a)** ..... **6**

**Key Features of an eERA Program under amended regulatory guidelines (Situation 2b)** ..... **7**

## Objective

eERA stands for 'extended' Environmental Risk Assessment. It provides a mechanism for ongoing environmental review post-marketing authorisation (MA) approval for new APIs authorised since 1st December 2006, a framework considering the total risk of all medicinal products containing the same API and a commitment from industry to follow up on new scientific information and identified risks in a responsible fashion. If an environmental risk is identified after the MA, an extended ERA process can provide a way to follow up on any additional studies agreed with the regulator in order to investigate, refine and resolve risks identified by the original ERA, and to evaluate the ERA, for example periodically based on new data available for the total use of the active pharmaceutical ingredient (API) and for its environmental concentrations and effects.

## Introduction

### The Inter-Association Initiative on Pharmaceuticals in the Environment (IAI PIE)[1]

EFPIA, EGA and AESGP recognise stakeholder concerns around pharmaceuticals in the environment (PIE) and are keen to participate in ongoing discussions in support of the European Commission developing PIE strategy. eERA is a key part of industry's 'Eco-Pharmaco-Stewardship' (EPS) proposal that will result in a refined, extended, where needed further strengthened, environmental risk assessment of pharmaceuticals in the EU.

eERA also addresses several of the key areas of concern regarding PIE. Specifically, it provides a collaborative framework to;

1) Reaffirm industry's commitment to robust ERA supporting the use of a product

2) Ensure compliance with post-approval ERA commitments

3) Undertake ongoing ERA review of pharmaceuticals post-approval and launch

4) Consider the total risk from all products containing the same API

5) Identify risk refinement options and generate new data where there are identified environmental risks

6) Follow up responsibly with appropriate risk mitigation measures where necessary

[1] The Inter-Association Initiative on Pharmaceuticals in the Environment (IAI PIE) combines the expertise of the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries and ssociations (EFPIA), and the European Generic and Biosimilar medicines association (EGA), in order to address the emerging environmental concerns.

## How eERA will work

At the highest level, eERA is a simple concept. The ERA of all 'new' APIs authorised after 1 Dec 2006 would be reviewed periodically throughout the life of the API. The focus on APIs (instead of medicinal products) is deliberate. It allows for a holistic assessment of total exposure resulting from the use of all medicines containing the same active ingredient.

The following situations illustrate how eERA would be applied in different scenarios of prior/post patent expiry and to those APIs that have been authorised prior to 1st Dec 2006.

**Situation 1: New APIs prior to patent expiry**

Before the patent expires and only one medicinal product is on the market consisting of a certain API, it would be up to the holder of the market authorization(s) to follow up on any additional studies agreed with the regulator in order to investigate, refine and resolve risks identified by the original ERA, and to evaluate the ERA based on new data available for the total use of the API and for its environmental concentrations and effects. This could include environmental data published by external researchers. Eventually, most of this information and the PEC/PNEC ratio for all indications with the same API would be summarized in the latest ERA and represented in the EPAR/PAR for the last authorised indication. It needs to be further explored if the environmental data presented in EPARs (centrally approved products) or PARs (nationally approved products) could be rendered more accessible.

eERA for the new APIs could be a voluntary process, which would rely on participation of MAHs and EMA/National Competent Authorities, with support from EFPIA, EGA and AESGP, or it could become an extended part of the regulatory reviewed ERA process of EMA or NCAs, whilst still ensuring that important new medicines continue to be routinely available to patients.

Before patent expiration, MAHs would be responsible for refining and resolving any risks identified from the original ERA, and for periodically evaluating the ERA based on new data available for the total use of the API and for its environmental concentrations and effects. If specific environmental risks are identified, it is anticipated that these would be summarized in any ERA updates for line extensions or Type II Variations. In exceptional cases where significant environmental risks are identified, there also already exists a mechanism for MAHs to submit a stand-alone ERA as a Type 1b Variation[2].

**Situation 2: New APIs after patent expiry**

After patent expiration, according to the suggested eERA scheme, the medicinal products containing the same API of all MAHs would contribute to the input of this substance in the environment. Thus, there would be two options how to proceed in this case.

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[2] Reference:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/07/WC500146564.pdf

**a) Voluntary review process:** All MAHs could collaborate to update the originator's ERA based on total use of the API if needed, due to increased generic medicines use or due to new indications. The process could start by referencing the PEC:PNEC in the latest approved ERA. At some agreed time point after patent expiry a review would be undertaken of the PEC (based on total API use) and the PNEC (taking into account any relevant new company or published data). If the 'new' PEC:PNEC is greater than 1 then all MAHs could collaborate to investigate, refine and resolve any new identified environmental risks. In this circumstance (anticipated to be for ←5% of APIs), some sufficiently transparent mechanism will be needed to review the detail of all available data, but without compromising data confidentiality or allowing inappropriate use of company confidential information. If the 'new' PEC:PNEC is less than 1 then no further action is needed and access to confidential data would not be an issue. The coalition would be responsible for the periodic review of any relevant newly published or internal data that becomes available, and voluntary submission of any environmentally significant findings. Again, if risks are identified during the periodic review under this voluntary eERA process, MAHs would submit the amended ERA via a Type 1b variation.

**b) Regulatory triggered process:** As an alternative to the above process, a new regulatory submission would trigger the requirement to review the existing ERA based on the (updated) total use (total PEC) of the API. The eERA scheme process could then be used individually by each MAH after patent expiration. In a situation when multiple products are authorised and there is an identified risk for an environmental impact for a certain API, an applicant could choose to share the work to address the possible environmental impact with other applicants and submit a common, updated ERA.

Under current guidelines, in a situation when the patent from the originator's product has expired, an ERA is only required for a new indication or due to estimation of increased amounts of APIs being used for existing indications. For generic medicines applications there is generally no anticipated significant increase to be forecasted after launch, the amount being used is typically substituting the amount of the originator medicine for some years, consequently no ERA is generally needed at the time of generic medicines application submission.

The current ERA guideline could be amended to require the ERA to cover the total amount of API being used for all indications. In this case, the ERA for the new indication would be the responsibility of the applicant alone and would need to be undertaken by each applicant. Under the current legislation cross-reference to the originator medicine's data is not possible so this would mean that all MAHs would theoretically have to generate their own data for their ERA. Clearly, this would result in duplicate testing. In the long term, and in order to avoid redundant environmental testing, it would be a preferred option to allow the applicant to reference environmental information and the PEC/PNEC ratio in the latest existing ERA (as summarized in the EPAR/PAR) as a starting point to address any additional environmental issues raised by the new indication or the increased use of the API.

When the existing PEC/PNEC ratio is low enough to accommodate additional uses with no additional testing, this would result in only a brief environmental summary referencing the EPAR/PAR

information. Again, after patent expiration, all individual MAHs could be required to periodically review and submit new environmental data or use information that presents significant issues for the ERA summarized in the latest EPAR/PAR published for one API.

**Situation 3: Legacy APIs/medicinal products authorised prior to Dec 2006:**

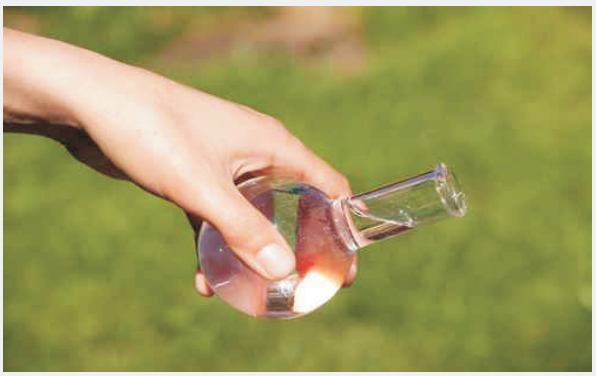
Medicinal products containing legacy APIs (i.e. products authorised prior to Dec 2006) are not in the scope of the proposed eERA approach. A separate approach is already under preparation as one of the projects (iPiE) of the IMI initiative. Industry and concerned NCAs work together to develop predictive frameworks that utilize information from existing datasets to support more risk-based testing of active pharmaceutical ingredients. Based on these results, legacy APIs will be classified and ranked to ensure that a full ERA will be performed in all cases where it is indispensable and/or environmental (bio) monitoring will be started if deemed necessary.

## Key Features of a prioritised eERA review Program (Situation 2a)

- The proposed voluntary and collaborative initiative would not require changes to existing legislation or guidelines (there is no need to amend the medicines legislation or guidelines to implement a voluntary eERA program)
- Relies on participation of MAHs and EMA/NCAs and support from EFPIA, EGA and AESGP member companies.
- Resides outside the risk-benefit assessment of the medicines legislation, thereby assuring patient access to medicines, but allows identified environmental risks to be addressed responsibly and collaboratively.

- eERA should be based on 'Total Predictive Environmental Concentration (PEC). Consequently all products containing the same API should be included to ensure that the total risk of a specific API is evaluated.
- Applies to all 'new' APIs contained in medicines first authorised in the EU after 1 Dec 2006. Legacy products authorised prior to 1 Dec 2006 will be addressed separately under the IMI initiative iPiE and prioritised APIs will be incorporated – if at all – in to the proposed eERA approach at a later date (see option 3 described above).
- Level of activity and effort required will be proportionate to the significance of identified risks (e.g. only APIs with PEC:PNEC $\geqslant$ 1 based on 'Total PEC' would be considered for further risk refinement measures that may be required.
- The proposed eERA approach would reside outside the current regulatory framework. Nonetheless, a mechanism already exists (via Type 1b Variation) in case a company wishes to submit a stand-alone amended ERA.

## Key Features of an eERA Program under amended regulatory guidelines (Situation 2b)



- Resides outside the risk-benefit assessment of the Medicines legislation, thereby assuring patient access to medicines, but allows identified risks to be addressed responsibly
- eERA should be based on 'Total PEC', i.e. encompassing all products containing the same API. A change in the ERA guideline, or its interpretation, could require the ERA to be based on the "Total PEC" for all uses of the API.
- Requires periodic evaluation of new environmental data once MA is granted and each specific medicinal product is marketed. This approach would require changes in the current ERA guideline although a different interpretation of the current wording could be reflected in the updated ERA Q&A document.
- Allows use of an EPAR/PAR summary of the latest ERA for an API, as a starting point for an ERA submission for a generic marketing authorisation would require at least a change in current guidelines, but as mentioned above could also be addressed by updating the current ERA Q&A paper as a quicker and easier implementation tool.
- Applies to all 'new' APIs contained in medicinal products authorised in the EU after 1 Dec 2006. Legacy products authorised prior to 1 Dec 2006 will be addressed separately under the IMI initiative and prioritised APIs will be incorporated – if needed – into the proposed eERA approach at a later date.
- Level of activity and effort required will be proportionate to the significance of identified risks (e.g. only APIs with PEC:PNEC $\geqslant$ 1 based on 'Total PEC' would be considered for further environmental risk refinement in the context of eERA)
- eERA responsibility is the responsibility of each MAH, but work can be shared if desired and a proper work-sharing framework is provided. An amended ERA could be submitted via Type 1b Variation, a provision that is already in place today.

AESGP

AESGP, the Association of the European Self-Medication Industry, is the representation of manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe. It is composed of national associations and the main multinational companies manufacturing self-care products. AESGP is the voice of more than 2,000 companies operating in the consumer healthcare sector in Europe, affiliated with AESGP directly or indirectly through the national associations.

www.aesgp.eu

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efpia

European Federation of Pharmaceutical Industries and Associations

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 40 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.

www.efpia.eu

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better access. better health.

Medicines for Europe represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members employ 160,000 people at over 350 manufacturing and R&D sites in Europe, and invest up to 17% of their turnover in medical innovation. Medicines for Europe member companies across Europe are both increasing access to medicines and driving improved health outcomes. They play a key role in creating sustainable European healthcare systems by continuing to provide high quality, effective generic medicines, whilst also innovating to create new biosimilar medicines and bringing to market value added medicines, which deliver better health outcomes, greater efficiency and/or improved safety in the hospital setting for patients.

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