ECO-PHARMACO-STEWARDSHIP (EPS)

A HOLISTIC ENVIRONMENTAL RISK MANAGEMENT PROGRAM

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Executive Summary

The pharmaceutical industry recognizes and understands concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment (PIE). The major source of pharmaceuticals entering into the environment is via patient excretion following use of medicine that is taken to prevent, cure or alleviate a medical condition. A comparatively smaller contribution to PIE, stems from emissions from industry during manufacture of the pharmaceuticals. Industry is committed to playing a role in addressing PIE concerns and is actively engaged in minimising the impact of its activities on the environment.

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 Associations (EFPIA), and the European Generic and Biosimilar medicines association (EGA), in order to address the emerging environmental concerns. This is being done through sound assessment of current and future actions, whilst remaining mindful of patient needs and ensuring access to medicines. Founded on the principles of product stewardship, the Eco-Pharmaco-Stewardship (EPS) initiative has been developed. It considers the entire life-cycle of the medicine and addresses the roles and responsibilities of all parties involved including public services, the pharmaceuticals industry, environmental experts, doctors, pharmacists, and patients.

The EPS initiative is supported by three 'pillars', which have been identified as the initial key areas of focus for the pharmaceutical industry:

- Pillar 1 – IMI iPIE project: The identification of the potential environmental risks of existing and new active pharmaceutical ingredients (API) through intelligent and targeted assessment strategies;
- Pillar 2 – Manufacturing effluents management: The compilation of best industry practices enabling manufacturers to minimize risks to the environment; and,
- Pillar 3 – extended ERA: The refinement of the existing environmental risk assessment (ERA) process for medicinal products to ensure that they remain up-to-date and relevant.

Pillar 1: The European pharmaceutical industry has initiated a project under the Innovative Medicines Initiative (IMI), a joint undertaking between the European Commission (EC), academia and the pharmaceutical industry. The project will use all available scientific knowledge to develop tools and assays, which will prioritize and identify the pivotal areas where more data would strengthen the understanding of a potential risk for medicinal products in use today, enabling the most efficient and effective use of resources. It is anticipated that the output may also be applied to screen new active pharmaceutical ingredients in development to target environmental testing needs.

Pillar 2: For the most part, the processes used to manufacture medicinal products are largely similar wherever in the world they may be used. It therefore follows that potential losses into the environment from manufacturing facilities should also be equally controllable. However, this assumes that a good understanding of the risk to the environment and the knowledge required to limit losses are uniformly available. In an effort across the industry, experts from several major manufacturers have shared experiences and developed a "maturity ladder" and associated guidance, in order to enable an enhanced understanding of the existing methods and the potential need for specific methodologies relative to the potential environmental risk posed by APIs and/or manufactured medicinal products. Manufacturing companies were encouraged to exchange practices in further developing their level of effluent control systems.

Pillar 3: An important cornerstone of EPS is a refined Environmental Risk Assessment (ERA) process, extending beyond marketing authorisation. The ERA of a medicinal product is currently performed by companies either as part of a new marketing authorisation or when an increase in the environmental exposure is expected, e.g. with the approval of a new indication or the inclusion of a new patient population. ERA must be performed to evaluate potential risks of medicines on the environment and ensure adequate precautions are taken where specific risks are identified. The extended ERA (eERA) includes provisions to:

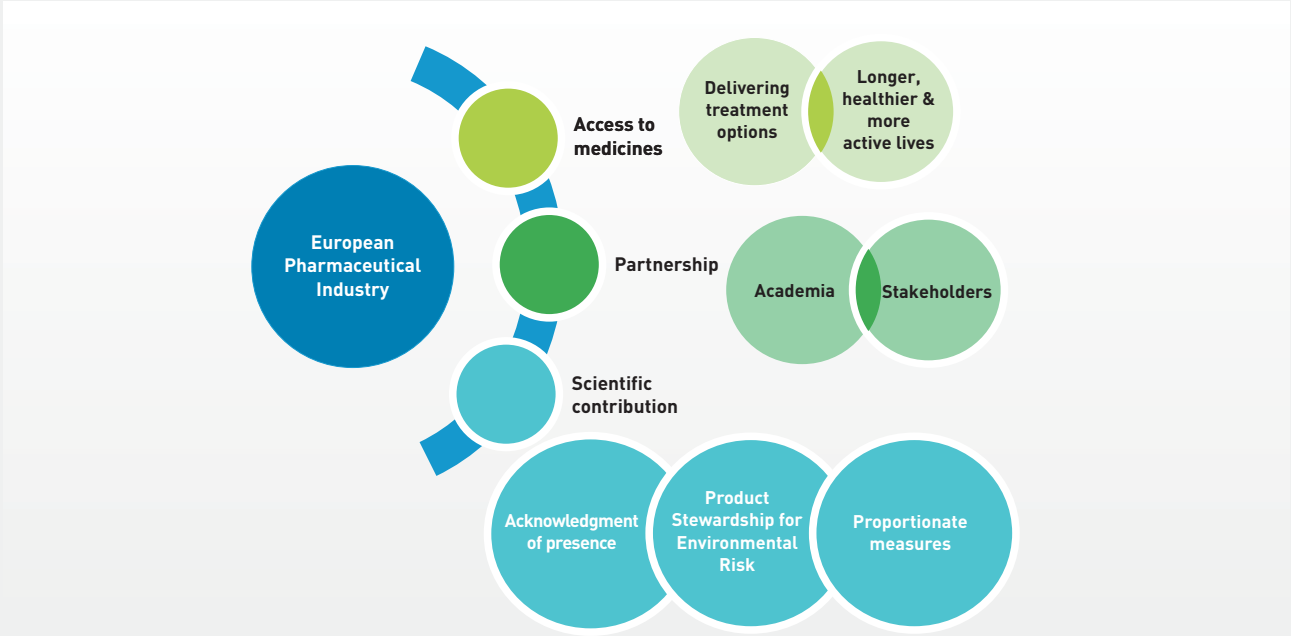
(i) adjust exposure predictions as usage figures become available to better reflect reality, including all products with the same API, and

(ii) reconsider the effects profile, as relevant and reliable laboratory findings and/or observations in the field linked to an adverse outcome become available.

The need for diligence does not end with the EPS pillars; there are many other opportunities to minimize losses to the environment along the life-cycle of a medicinal product, such as increasing transparency of the environmental data, and educating the public on the correct use and disposal of medicines. The pharmaceutical industry stands ready and willing to work with other stakeholders in evaluating and working on these. In all of these endeavours, the key priority remains to ensure patients' access to medicines in cooperation with all stakeholders, including European and National Competent Authorities. The industry believes that the EPS approach can serve to address concerns and adequately inform the existing regulatory paradigm.

The European Pharmaceutical Industry's Role and Mission in the Field of Pharmaceuticals in the Environment (PIE)

The European pharmaceutical industry acknowledges the concerns of stakeholders as to the emergence of pharmaceuticals, among other man-made chemicals, as micro-pollutants in the environment and more specifically in water. We aim to play an active and focused role in developing science-based measures to minimise the impact of our activities and products on the environment.



Access to medicines is paramount for patients and society. Policy making on PIE must safeguard patient access to medicines. The industry focuses on delivering treatment options that allow people to live longer, healthier and more active lives. We aim to do this without compromising our responsibility to minimize the impact on the environment, by playing an active role in helping develop proportionate and science-based measures to protect the environment against any direct or indirect impacts of our work in bringing life-changing medicines to patients. The pharmaceutical industry supports greater efforts in understanding the long-term potential environmental impact of medicines. The industry has been, and continues to be, a significant party to the scientific discussion on PIE with numerous PIE-related publications in the last decade.

AESGP, EFPIA and EGA have jointly developed the EPS initiative as a platform for discussions with stakeholders on PIE, more information is presented in the following sections.

This document focuses on human medicines only; veterinary medicines, vitamins[1], minerals[1], herbal medicines[1] and homeopathics[1] are not included in the scope of the EPS initiative.

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[1] EMA Environment Risk Assessment Guideline, EMEA/CHMP/SWP/4447/00 corr 2, June 2006
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf
"In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment. The same applies to vaccines and herbal medicinal products."

Eco-Pharmaco-Stewardship (EPS) - Overview

Application of the EPS approach to the Medicinal Product Life-Cycle

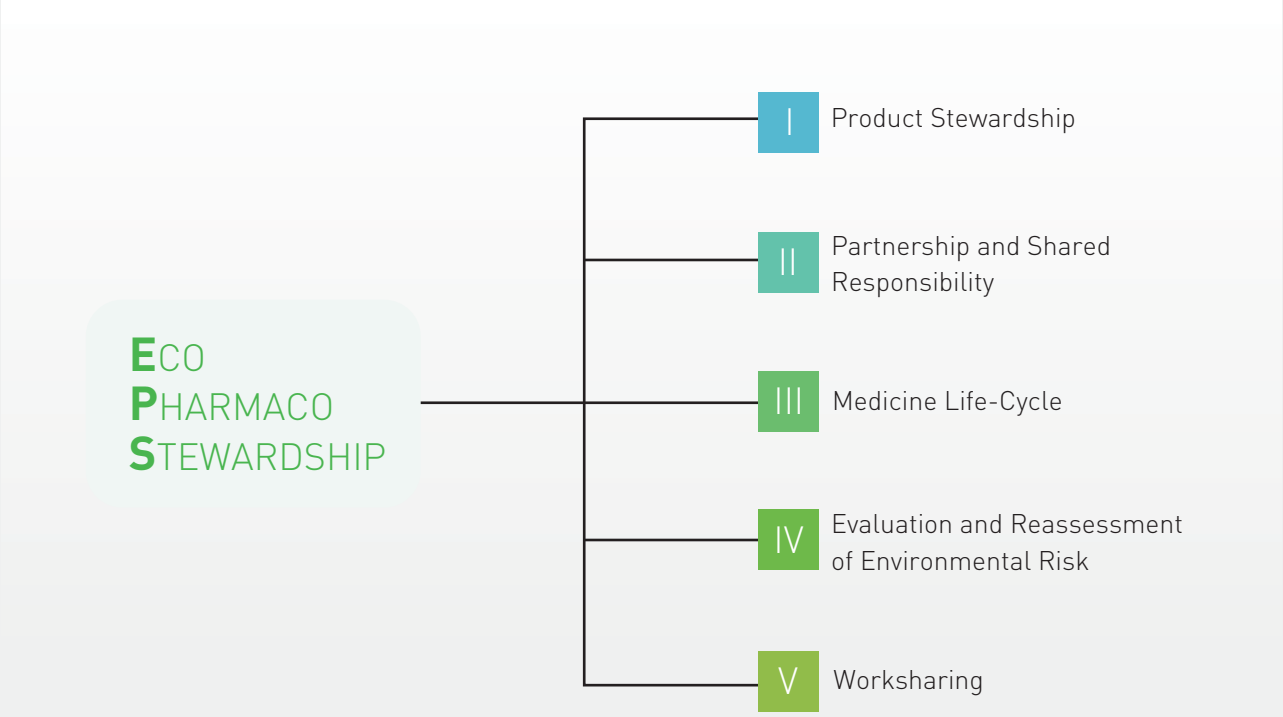
EPS focuses on stewardship priorities where the pharmaceutical industry can most effectively reduce the potential environmental risks that might result from its activities and throughout the medicinal products life-cycle.

The proposal strives to protect patients' access to medicines while appropriately considering potential environmental impacts. Most aspects of EPS are readily implementable under the current pharmaceutical legislation, thus preventing the need for additional regulation and changes in other policy areas.

EPS Concept[2]

The European pharmaceutical industry takes PIE concerns very seriously. The industry believes the overarching framework and integrated approach of EPS can serve as the foundation for a successful European strategy on PIE, whilst also having positive effects globally.

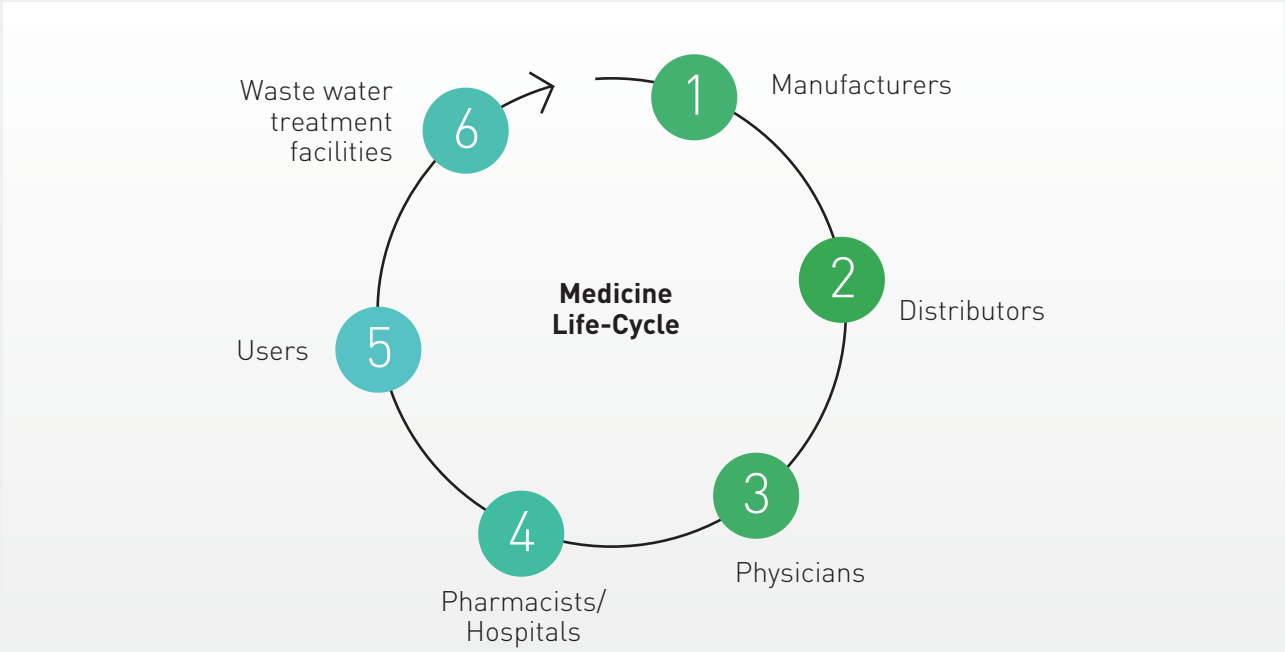
The EPS initiative is underpinned by a number of key principles: product stewardship, partnership and shared-responsibility, medicine life-cycle, evaluation and re-assessment of environmental risk, worksharing.



[2] The EcoPharmacoStewardhip approach was first described by David Taylor in 2010 in a chapter Green and Sustainable Pharmacy (Edit:Kümmerer & Hemple, Pub: Springer). The industry proposal applies the original EPS in a broader scheme. Reference: D. Taylor (B), WCA Environment Limited, Oxfordshire SN7 7YR, UK, Chapter 7 - Ecopharmacostewardship – A Pharmaceutical Industry Perspective, In: K. Kümmerer, M. Hempel (eds.), Green and Sustainable Pharmacy, DOI 10.1007/978-3-642-05199-9_7, C Springer-Verlag Berlin Heidelberg 2010

Product stewardship[3] in general can be defined as a product-centric approach to environmental protection. All actors in the product life-cycle - manufacturers, retailers, users and disposers (i.e. upstream and downstream users) - work **in partnership to share responsibility** for reducing the environmental impacts of medicinal products at each of the key stages.

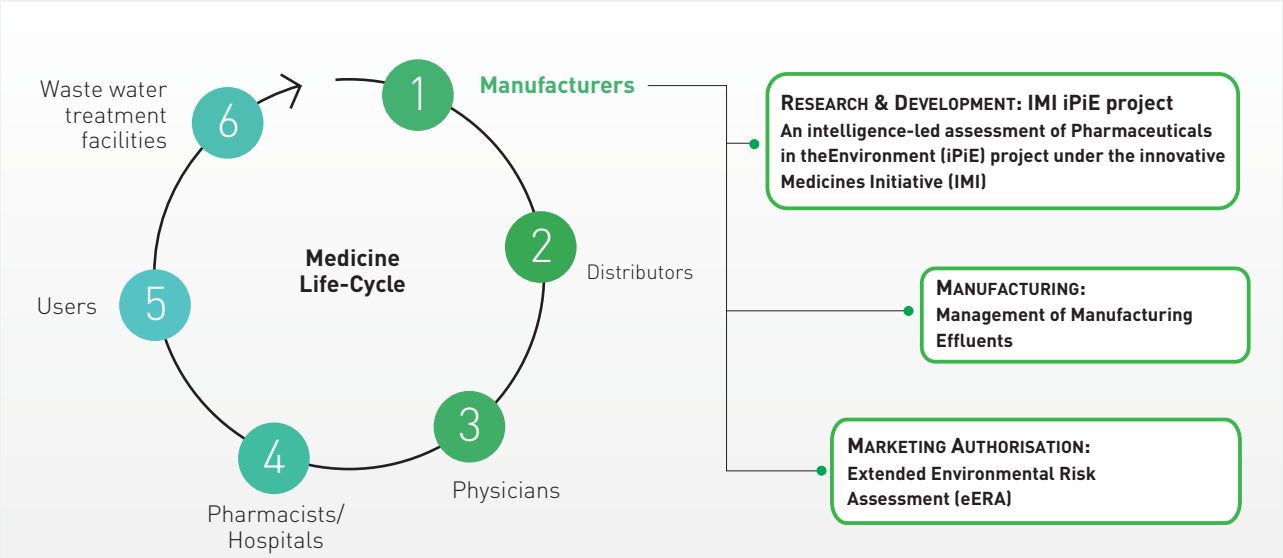
The **Medicine Life-Cycle** involves a range of upstream and downstream users. Essentially, interest in the continuation of environmental risk management from product development through approval and use represents an environmentally-focused version of the product stewardship paradigm.



At the pharmaceutical development and manufacturing stages, industry is playing an active role in developing and maintaining a system that ensures a sound, scientifically based regime for **evaluation and re-assessment of environmental risks**. This would take into account scientific advancement in ERA, changing use patterns, market growth, etc. It establishes refinement of ERA in the post-approval phase of the medicines authorisation process, where warranted, under the current legislative framework, and ensures patients' access to medicines remains unimpeded. It operates on the basis that initially the originator company would be responsible, but as other competitors enter the market, **work/cost sharing** among companies could take place.

[3] Definition from the USA Environmental Protection Agency
http://archive.epa.gov/wastes/conserve/tools/stewardship/web/html/index.html

EPS - Priority Areas of Focus for the pharmaceutical industry



PILLAR 1 - Research & Development: Intelligence-led Assessment of pharmaceuticals in the Environment (iPiE)

The pharmaceutical industry is actively engaged in scientific research projects (independently and in partnership) aimed at filling the priority knowledge gaps in order to support informed science-based policy making on PIE. The industry supports further scientific study, to better understand the implications of trace amounts of pharmaceuticals on the environment. We are actively engaged on this issue as individual companies and in cooperation with other interested partners in academia, industry and government. For further details, see Appendix 3 .

Under the Innovative Medicines Initiative (IMI) - the public-private partnership between EFPIA and the European Commission - the industry has initiated iPiE (Intelligence-led Assessment of Pharmaceuticals in the Environment). iPiE is a four-year, over 10m€ collaboration project between industry, academia and regulators which is primarily aimed at developing and validating models that will enable:

(i) Focused environmental fate and effects testing of potential high risk substances (both for new and existing substances), and,

(ii) Early identification of pharmaceutical substance properties and the associated environmental risk potential.

The project is expected to be completed by the end of 2018.

Expected Benefit:
A better understanding of the relative risks posed by pharmaceuticals in the environment. Tools to screen and prioritise new and existing products for a definitive ERA.

PILLAR 2 - Manufacturing: Effluent Management

The overall contribution of pharmaceutical manufacturing to the amounts of PIE is relatively low compared with those from other sources, e.g. patient excretion during normal use of medicine[4]. However, there is the potential for localised impacts to be created in cases where manufacturing emissions are inadequately managed.

Ensuring use of appropriate environmental risk management measures to adequately control manufacturing effluent emissions remains an important area of focus for the pharmaceutical industry and is an approach already in place in a number of companies.

In 2011, a group of environmental specialists from the pharmaceutical industry met for a two-day workshop to compare and compile approaches to risk identification and effluent management. Since then, additional work has occurred and a paper (described in Appendix 4 of this document) was produced that includes both industry practices and a 'maturity ladder' aimed at helping companies to gauge their performance. Simply put, a maturity ladder is a stepwise approach of increasing capability, whereby sites progress from implementing the minimum requirements to legally operate the facility and advance to assessing and managing risk to the supply chain from potential API discharges from the facility. A few sites may progress to mature facilities that benchmark practices with peers. As an example, if continuously monitored evidence suggests that a given substance presents a risk to the environment, progress on the maturity ladder may be deemed necessary. Moving on to the next level of the maturity ladder may include undertaking improvement measures, such as establishing exposure standards, evaluation of emissions, and consideration of enhanced control measures where needed.

The pharmaceutical industry engages in developing and implementing initiatives, which minimise API discharges from manufacturing operations through the exchange of practices.

Alongside and as a complement to the above, the industry is working collectively on improving the EHS performance of its supply chain. There are a few projects already running, e.g. the Pharmaceutical Supply Chain Initiative[5] (PSCI). Besides, the industry continues to make progress in this regard.

Expected Benefit:
Broaden awareness, share practices and provide guidance resulting in improved performance of the management of manufacturing effluent.

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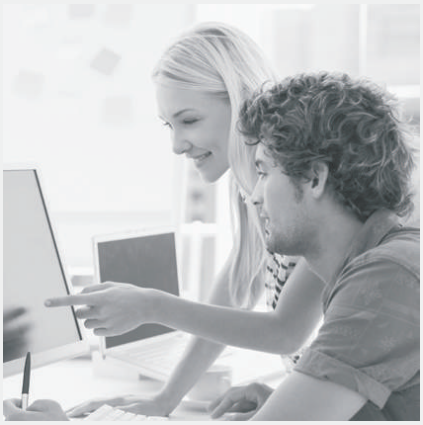
[4] Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters - KNAPPE report 2008, http://environmentalhealthcollaborative.org/images/KNAPPE_REPORT_FINAL.pdf
"[...] it is generally accepted that emissions from pharmaceutical manufacturing are negligible especially in Europe and the North America (in Asian countries concentrations discharged for single compounds can be up to several mg L-1). On the contrary, excretion by patients in private households has been found to be the most important source of discharge in the environment"

[5] http://pharmaceuticalsupplychain.org

PILLAR 3 - Marketing Authorisation (MA) : Extended Environmental Risk Assessment (eERA)



The environmental risk assessment (ERA) of medicinal products, has been submitted by companies as part of the marketing authorisation application of new medicinal products since 2006. The ERA is performed to evaluate potential risks of the API of the medicinal product on the environment and to ensure adequate precautions are taken where specific risks are identified.

The current approach involves forecasting usage prior to the actual use to determine a Predicted Environmental Concentration (PEC) and uses the results of toxicity studies to derive the Predicted No-Effect Concentration (PNEC). The two values are compared and, if the PEC is less than the PNEC the predicted environmental risk is considered to be low.

Typically, the ambiguity arises when external research, performed after the medicinal product authorisation, identifies a potential for refinement of the ERA based on new scientific knowledge compared to that considered in the initial ERA. While there is a regulatory requirement to update an ERA if a new application increases the environmental exposure (when the regulatory route to inform the authority would be to submit either a Type II variation or a line extension), there is currently no such requirement to update the ERA should such new scientific knowledge become available. There is provision to submit a standalone ERA 'in exceptional circumstances' as a Type IB Variation at any time, however there is no guidance as to what would trigger such action. Thus, if a significant risk were identified this could potentially be reported as a Type IB Variation. However there is currently no requirement or mechanism to identify any new information that might affect the risk assessment, and there is no guidance as to what action should be taken should a significant risk be identified.

As generic medicines enter the market after patent expiry of the original product, there is currently no mechanism to consider the cumulative effect of several medicinal products containing the same active pharmaceutical ingredient (API).

To address the above points the EPS approach proposes extending the ERA paradigm and including mechanisms throughout the product's life-cycle to refine usage figures, investigate effect concerns identified post-approval, and to follow up on any identified environmental risks appropriately. Should the ERA outcome change, environmental risk management measures could be put in place or adjusted, as necessary.

This extended ERA (eERA) would include:

1. Consideration of the Total PEC arising from all products containing the same active pharmaceutical ingredient.

2. Assessing the robustness of all research findings (internal and external), following up with additional laboratory testing where necessary, and assessing the likelihood that the research finding can translate into an adverse population level impact in the field.

3. If necessary, in cases where potential environmental risks are identified, looking for indicators of the effect on wildlife through targeted sampling where concentrations can be expected to be at their highest.

4. Under the auspices of the EMA/national competent authorities and other stakeholders (including concerned companies), develop suitable and proportionate environmental risk management measures where needed.

5. Utilizing the prioritisation tools from IMI project iPiE to identify gaps for legacy APIs. In cases where gaps are found, utilizing the eERA process to determine applicable risk management measures.

Any significant environmental risk identified once a medicinal product is placed on the market would trigger appropriate further work to refine the ERA. Conversely, where post-authorisation surveillance does not indicate any significant risk for an API, then no further action is needed until the review of the ERA based on Total PEC is conducted.

"Legacy" APIs / medicinal products (i.e. authorised prior to 1st December 2006 and lacking current ERA data) are not immediately in the scope of this eERA approach. A separate scenario is already under preparation as one of the projects (iPiE) of the IMI initiative intends to identify and prioritise these (described on page 9 of this document). The pharmaceutical industry and concerned stakeholders shall work together to develop predictive frameworks that utilize information from existing datasets to support more intelligent environmental testing of APIs where needed.

Expected Benefit:
The eERA concept addresses questions from scientific, environmental and economic perspectives as it takes account of all products containing the same API and calls for risk management resource deployment as and when a risk is established. eERA will also improve the scientific rigor of the current ERA by ensuring that it reflects the latest published research findings (e.g. peer-reviewed publications).

[6] Article 127b, Directive 2001/83/EC, as amended reads: "Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired."

[7] Health Care Without Harm report on collection schemes https://noharm-europe.org/sites/default/files/documents-files/2616/Pharm%20Report_WEB.pdf

Beyond the pharmaceutical industry 'Focus Areas' - The appropriate disposal of unused and/or expired medicines

Estimates of the contribution of unused medicines to the overall occurrence of pharmaceutical residues in the environment can vary, but it is widely accepted that it is a minor contributor to the overall concentrations[4]. Nonetheless, it is similarly agreed that it is one of the contributing factors for PIE that can be directly acted upon.

Provisions already exist in the EU medicines legislation for Member States (MSs) to establish mechanisms for the appropriate collection[6] and disposal of unused medicines without specifying the nature of such schemes. This allows MSs to tailor implementation to national needs and existing infrastructures. In accordance with the legislation, nearly all MSs have implemented national schemes to address local situations, all of which vary and present specificities[7].

The extent to which a collection system is used will depend very much on the level of awareness among patients. While EU MSs have the responsibility to set up and manage such collection schemes, all stakeholders including healthcare professionals have a role in educating patients about existing collection schemes and need to dispose of medicines in a careful and appropriate way. Collaborative discussion and action among stakeholders at EU and national levels could address this issue.

The pharmaceutical industry stands ready to support European and MSs' communication activities and awareness raising campaigns aimed at patients and public on the appropriate use, storage and disposal of medicines. A social media campaign #medsdisposal on the appropriate disposal of medicines was launched in June 2015. This is a joint initiative between European healthcare, industry and student organisations. Further information is available at http://medsdisposal.eu/

Expected Benefit:
Increased patient knowledge of the appropriate disposal of expired and unused medicines.

List of Abbreviations

AESGP	Association of the European Self-Medication Industry
API	Active Pharmaceutical Ingredient
EC	European Commission
eERA	extended Environmental Risk Assessment
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic Medicines Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPS	Eco-Pharmaco-Stewardship
EU	European Union
IAI	Inter Association Initiative (in the context of collaboration between industry associations)
IMI	Innovative Medicines Initiative
iPIE	Intelligent led assessment of pharmaceuticals in the environment
MA	Marketing Authorisation
MS	Member State
NCA	National Competent Authorities
OECD	Organisation for Economic Cooperation and Development
PEC	Predicted Environmental Concentration
PIE	Pharmaceuticals in the Environment
PNEC	Predicted No Effect Concentration
PSCI	Pharmaceutical Supply Chain Initiative
SME	Small and Medium sized Enterprises

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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medicines for europe
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.

www.medicinesforeurope.com

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