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Improving the regulatory environmental risk assessment of human pharmaceuticals: Required changes in the new legislation

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ABSTRACT

One of the flagship actions of the Pharmaceutical Strategy for Europe is to address environmental challenges associated with pharmaceutical use. This includes strengthening the Environmental Risk Assessment (ERA) at marketing authorisation (MA) of pharmaceuticals, and revision of the pharmaceutical legislation where needed. The overall aim of an ERA should be to enable comprehensive and effective identification and management of environmental risks of pharmaceuticals without affecting the availability of pharmaceuticals to patients. As experts in the evaluation of ERAs of human medicinal products submitted by pharmaceutical industries (Applicants), we have summarized the current status of the ERA and suggest legislative changes to improve environmental protection without affecting availability. Six regulatory goals were defined and discussed, including possible ways forward: 1) mandatory ERAs in accordance to the EMA guideline at the time of the MA, 2) enforcement of risk mitigation measures including re-evaluation of the ERA, 3) facilitated exchange of environmental data between pharmaceutical and environmental legislations, 4) substance-based assessments, 5) transparency of data, and 6) a catching-up procedure for active pharmaceutical ingredients that lack an ERA. These legislative proposals can be considered as prerequisites for a harmonised assessment and effective management of environmental risks and hazards of human pharmaceuticals.

1. Introduction – problem statement and aim

After pharmaceuticals are used by patients, some of their residues end up in surface waters and soils. This leads to concentrations of pharmaceuticals in the environment that may pose a risk to ecosystems, contribute to the spread of antimicrobial resistance (AMR) and contaminate drinking water sources (Tyler and Goodhead 2010; WHO 2017; Miller et al., 2018; OECD 2019; Larsson and Flach 2022). The highest concentrations are most often found in countries with limited sanitation (aus der Beek et al., 2016; Wilkinson et al., 2022). However, a lack of ecotoxicity data for a large number of pharmaceuticals hampers a thorough assessment and quantification of the potential environmental impacts (Gunnarsson et al., 2019).

In 2019, the European Commission adopted the European Union Strategic Approach to Pharmaceuticals in the Environment (European Commission, 2019d). The approach includes proposals to reduce the risks from pharmaceuticals and their residues to and via the

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Abbreviations

AESGA	Association of the European Self-Care Industry
AMR	Anti-microbial resistance
API	Active pharmaceutical ingredient
B/R	Benefit/risk
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generics Medicines Association; now: Medicines for Europe
EMA	European Medicines Agency
(E)PAR	(European-) Public Assessment Report
EQS	Environmental Quality Standard
ERA	Environmental risk assessment
EU	European Union
MA	Market authorisation
PBT	Persistent, bioaccumulative and toxic
WFD	Water Framework Directive

environment. The following challenges were identified: strengthening the Environmental Risk Assessment (ERA), enforcing risk mitigation, increasing data transparency, closing data gaps and controlling the production of pharmaceuticals. Some of the shortcomings mentioned can be partly addressed by non-legislative actions (national activities or projects at EU level), but others require changes in the current legislation. Consequently, environmental issues are one of the flagship initiatives in the Pharmaceutical Strategy for Europe (European Commission, 2020b) and are mentioned in the impact assessment for the new pharmaceutical legislation (European Commission, 2021a).

The ongoing revision process of the pharmaceutical legislation combined with the EU initiatives on Zero Pollution (European Commission, 2021c) and the Chemicals Strategy (European Commission, 2020a) with the One Substance-One Assessment Approach (OSOA), brings opportunities for strengthening the ERA requirements and its consequences, so that environmental impacts due to the use of medicines can be reduced. The European Parliament also called on the Commission to strengthen the ERA, provided that marketing authorisations (MA) are not delayed or refused solely on the grounds of adverse environmental impacts (European Parliament, 2019).

In the EU, according to Article 8 (3) (ca) of Directive (2001)/83/EC an ERA is to be submitted as part of all new medicinal product MA applications. However, no further details are provided in this Directive on protection goals and what an ERA should constitute. What is clear from the Directive is that any risk of undesirable effects on the environment is not part of the benefit/risk (B/R) balance of the medicinal product and thus a refusal of the authorisation because of ERA issues is not foreseen in this current legislation. As a consequence, a lack of environmental data or insufficient risk mitigation cannot be a reason to deny MA or to impose mandatory risk mitigation measures. Within the regulatory MA procedure, this means that ERA issues do not have the same priority as efficacy or patient safety.

The EU "Guideline on the environmental risk assessment of medicinal products for human use" from 2006 (EMA 2006; Spindler et al., 2007) and the related Questions & Answers document (EMA 2016), give instructions to the Applicants on how to conduct the ERA and to regulatory assessors on how to evaluate the ERA submitted by the Applicants. An ERA is required for all active substances, except for naturally occurring substances such as vitamins, electrolytes, proteins, and amino acids. The assessment itself is a stepwise procedure. Phase I is a screening phase to determine whether a further assessment is needed for PBT criteria (persistence, bioaccumulation and toxicity) or risks (if the calculated environmental concentration is above a certain threshold value and might cause adverse environmental effects). In these cases, a Phase II environmental effects and fate assessment is required with a range of Good Laboratory Practice-compliant studies on ecotoxicity (algae, daphnia and fish) according to Organisation for Economic Co-operation and Development (OECD) test guidelines (TG) and on physico-chemical behaviour in environmental compartments including sewage treatment (adsorption-desorption, biodegradation) (OECD 1992; OECD 2000; OECD 2002; OECD 2011; OECD 2012; OECD 2013). Currently, the ERA guideline is under revision (Whomsley et al., 2019) aiming to update scientific approaches and testing strategies. As protection goals were not defined in the legislation, the guideline translates the ERA in a relatively narrow manner: in the current as well as the draft new versions of the guideline, the ERA exclusively covers the impact of the use of a medicinal product. It does not take into account emissions at production sites and the waste coming from the medicinal product packaging, and is a product-based assessment of its active pharmaceutical ingredients (APIs), that are meant to exert the biological effect in the patient. The current ERA only deals with risks to environmental organisms, but not to humans (via drinking water or fish consumption), and also disregards AMR.

For medicinal products authorised before 2006 (so-called legacy products), often no ERA has been performed. On the German market, ERA data are missing for 281 out of 404 APIs for which risks cannot be ruled out because of their (expected) environmental concentration (>0.01 μg/L based on consumption data) or because of specific substance characteristics, like endocrine activity (Gildemeister et al., 2022). Many of these APIs are legacy products with high use.

In October 2022, the European Commission proposed to place a number of pharmaceuticals on the Priority Substances list of the EU Water Framework Directive (WFD) (European Commission, 2022b) because of risks to the aquatic environment. This increases the urgency to deal with these substances. Currently, the burden of reducing these substances relies to a great extent on waste water treatment (EurEau 2021), since other risk mitigation cannot be enforced. Upgrading waste water treatment with advanced treatment steps is not always feasible nor sustainable in view of energy- and material use of these additional steps. Moreover, the limited accessibility of ERA data from the medicine authorisation process hampers their use for derivation of environmental quality standards under the WFD and other environmental legislative frameworks.

In this paper, we combine our 15+-years expertise as regulatory risk assessors and/or toxicologists to describe the current limitations of the legislative ERA framework for medicinal products and provide recommendations to improve the ERA and its consequences in the legal framework. Recently, the EU Commission published its proposal for a new Directive (repealing Directive, 2001/83/EC) and Regulation (repealing Regulation No. 726/2004) on the Union code relating to medicinal products for human use (European Commission, 2023a,b). The work of this publication was finished before the EU commission published the proposals. Therefore, further reference to the EU pharma package is not included. However, the recommendations made can be used in the legislative process and provide important background information. We describe this along 6 different goals, with a mission to minimise adverse environmental impacts due to the use of pharmaceuticals, without affecting the availability of needed pharmaceuticals for patients. The backbone of all proposed changes is that environmental risks due to the use of pharmaceutical products should be made transparent and mitigated as far as possible. This paper is accompanied by a paper that focusses on a framework for risk mitigation measures (Moermond et al., 2023).

In the following, the term active ingredient includes all substances in the product that exert a biological effect, i.e. the API and any active excipients. Furthermore, the term environmental risk includes a hazard assessment based on PBT data as well as a risk assessment (resultant of exposure and effects), in accordance with the ERA guideline (EMA 2006).

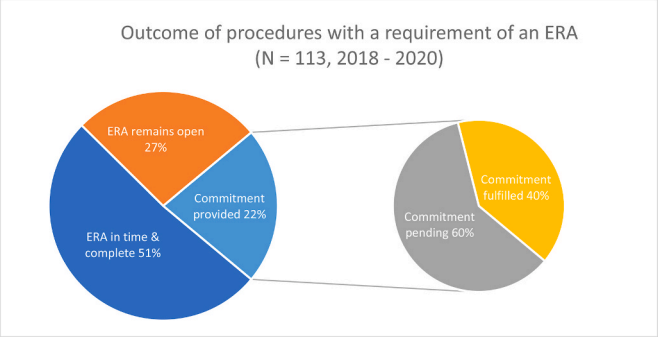

Fig. 1. Analyses of ERA conclusions in procedures with co-working of the German Environment Agency because environmental issues may be relevant. [1] Applications under Art 8 (3), Art 10-generic medicinal products, Art 10 (3)-hybrid, Art 10a-well established use/bibliographical, Art 10b fixed combinations, Art 10c informed consent and Art 10 (4) similar bio-logical applications where co-working of UBA was requested and Germany was Reference Member State.

2. Goals, current situation and change needed

2.1. Goal 1: The ERA is provided in time and complete at the time of marketing authorisation

A complete ERA at the time of MA is necessary to decide on appropriate mandatory risk mitigation measures. When ERA studies are provided in time, along with the other requirements of the MA application dossier, it is possible to make potential risk mitigation measures part of the MA and product information, and to ensure timely identification and publication of potential risks. Otherwise, products that pose a risk to the environment may be placed on the market without having appropriate risk mitigation measures in place.

A MA can be requested via a centralised procedure (EU-wide), a national procedure, or a decentralised/mutual recognition procedure (for some EU Member States). Although the majority of MA Applicants under the centralised procedure fulfil their obligations with regards to ERA at time of granting the approval (Caneva et al., 2014), to our experience this is often not the case with national or decentralised procedures (DCP) (see Fig. 1). To avoid delays in MA, it is common practice to grant a MA regardless of ERA issues. In Germany, 113 procedures which require an ERA in accordance to the EMA guideline were assessed between 2018 and 2020. In 49% of the cases no ERA was available at time point of MA. For more than a half of these procedures the ERA issue remained open until the end of the procedure and for the others a commitment of the applicant to conduct an ERA in an agreed time frame was provided. However, only 40% of them were fulfilled in the requested time frame at the end of 2022.

To enforce the submission of a complete, timely and satisfactory ERA dossier, we propose to revise the legislation to.

1. Introduce a stand-alone ground for refusal of the MA when risks to the environment and/or public health via the environment (including AMR) have not been sufficiently and satisfactorily addressed by the Applicant; and/or
2. Include the ERA outcome in the B/R balance as a complete data set is a pre-condition for such an evaluation.

To extend the current practice of balancing the B/R solely for patients (EMA 2018) to include environmental impact (both towards organisms in the environment as indirectly towards public health, e.g., via drinking water or food chain), guidance would be needed on how to do this. There might be the possibility in such guidance to define medicines where the health benefit will typically be much higher than the environmental harm e. g. life-saving pharmaceuticals for conditions with unmet medical needs.

SUMMARY OF PRODUCT CHARACTERISTICS

6. PHARMACEUTICAL PARTICULARS

6.6 Special precautions for disposal <and other handling>

<Any unused medicinal product or waste material should be disposed of in accordance with local requirements.>

LABELLING AND PACKAGE LEAFLET

5. How to store X

<Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.>

Fig. 2. Texts on disposal from the Quality Review of Documents (QRD) templates for Centralised Procedures.

These actions would mirror the approach taken in the new regulation of veterinary medicinal products, where a stand-alone ground for refusal has been added (Article 37 (2) (i) Regulation (EU) 2019/6) and environmental risk is still part of the B/R balance (Art. 4 (19) (b) EU 2019/6). For human pharmaceuticals, only one of the options would serve to enforce a timely and complete ERA. For both actions, exemptions for emergencies, e. g. a medicine introduced to combat a pandemic, should be possible.

Making environmental impact part of the B/R balance and/or a sole ground for refusal would emphasize the importance of the ERA and can make risk management mandatory.

For a decision about the environmental risk and risk mitigation, the ERA scope needs to be clearly defined by legislation. For details the ERA guidance published by the EMA should be used. Therefore, it needs to be specified in the legislation that the ERA guidance is legally binding. As for protection goals, both environmental and human health (effects via the environment) need to be considered. Finally risk mitigation measures must be set. Consideration should be given to the risks posed by active ingredients at manufacturing, use, and disposal. Therefore, it is suggested to streamline descriptions in the Annex with the veterinary legislation where the main protection goals are defined and the core structure of an assessment is addressed (European Commission, 2019c), including a short description of consequences of risk and hazard assessment. Technical guidance on how to perform this assessment should be updated to reflect all these aspects e. g. new requirements to consider the risks to human health via the environment. Clear descriptions in legislation and guidelines will make decisions on mandatory completeness possible.

2.2. Goal 2: Risk mitigation measures are mandatory in case of risk, including regular re-evaluation

Directive 2001/83/EC art 8.3 (ca) only requires the Applicant to provide an evaluation of the environmental risks as well as reasons for safety measures to be taken for the storage, administration to patients, and disposal of waste products: "*Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.*" In practice, this entails only a statement on disposal of the product, regardless of the outcome of the ERA. Such statements are placed in the summary of product characteristics, labelling and package leaflet, published on EMA or national websites (see Fig. 2).

According to art. 127b introduced in 2004 (Directive, 2001/83/EC), a reference to any appropriate collection system in place for medicinal products that are unused or have expired, should be included in the Blue

Box (i.e. at national level) on the outer packaging (European Commission, 2021b). Indeed, no harmonised EU legislation regulating left-over and expired pharmaceuticals disposal and waste management systems, is in place.

However, the majority of emissions into water systems originate from the excretion of medicinal products taken by patients (OECD 2019) and collection systems for unused products do not mitigate this risk. As described in an accompanying paper (Moermond et al., 2023), preliminary risk mitigation measures are applied when risks are determined based on model estimates, and definitive, more strict and far-reaching risk mitigation is applied when risks are based on actual measured environmental concentrations. All (new) information should flow into a re-evaluation of the ERA, needed to decide on further appropriate risk mitigation measures. Product-based risk mitigation measures should be designed to actually reduce environmental impacts, along the principles as previously laid down for veterinary pharmaceuticals (EMA 2012). This should be done within well-defined boundary conditions, as explained in Moermond et al. (2023). This applies to different stages in the product chain, like at prescription (preference for low-risk alternatives), supply (over the counter or not), use (collection of excreta) and even advertising. Besides this, risk mitigation should be harmonised between products with the same active ingredients, which may have to be enforced via a so-called referral procedure for products already authorised.

Thus, part of risk mitigation would be to monitor the use and/or environmental concentrations, leading to a re-evaluation of the ERA. To be able to do this on a case by case basis, Applicants need to provide data on use, facilitate monitoring if modelled exposure points based on market data are at risk (Moermond et al., 2023), and provide information on analytical techniques to water managers. This way, risks may be refined and mitigation options may be made more or less strict and far-reaching.

This re-evaluation should be a standard procedure for all products, but more often for products with a predicted or identified environmental risk. Besides this, re-evaluation should take all new information into account, including (monitoring) data from other (environmental) frameworks and new experimental studies reported in scientific literature. Thus, the legislation should be amended for a regular re-evaluation of the ERA (e.g., 5 years in case of risk, ad-hoc in case of new information that would change the outcomes of the risk assessment) (Moermond et al., 2023). The industry associations (EFPIA, AESGP, EGA) have proposed an eco-pharmaco-stewardship initiative - pillar 3 Extended Environmental Risk Assessment, in which a system is to be arranged to share data amongst Applicants and MA holders (Efpia 2015), followed by a regular re-evaluation. The industry proposal is endorsed; however, re-evaluation should not be voluntary, and still ensure that important new medicines continue to be routinely available to patients. The re-evaluation dossier should be the responsibility of the MA holder of the originator medicinal product within market exclusivity period. After expiry of patent(s) or another agreed time period, all MA holders (including of generics/hybrids/biosimilars) should contribute to the re-evaluation of the ERA. A monograph system (See goal 4) with data-sharing obligations could be used to accommodate this review.

2.3. Goal 3: pharmaceutical and environmental legislations are coupled

The use of pharmaceuticals may lead to risks to ecosystems. Therefore, it is important to bridge the gap between pharmaceutical and environmental legislative frameworks. Currently, no direct regulatory link exists between ERA results (as a part of MA) and the management of the environmental impacts after the product has reached the market (Freriks et al., 2010; Oelkers 2021). For example, when the outcome of an ERA indicates a risk or hazard to the environment, no legal obligations are in place to communicate this information to authorities responsible for environmental management such as water authorities. Besides this, reliable data on environmental fate and effects of APIs, as provided for the ERA, are very relevant for other environmental legislative frameworks like the WFD, its daughter directives, and the Urban Wastewater Treatment Directive. These data may be used in these frameworks to e. g., derive WFD environmental quality standards (EQS), for drinking water quality assessment, or assessment of the possibility to re-use treated wastewater for irrigation. Besides this, data generated within other regulatory frameworks such as the WFD could also be useful for the ERA as monitoring data could show whether concentrations leading to a predicted risk are actually found in the environment, and thus help to refine risk mitigation measures.

Recently, the European Commission has published draft EQS values (European Commission, 2022a) for a number of pharmaceuticals, to be taken up on the priority substances list. This means all EU Member States need to monitor the presence of these substances, and when concentrations exceed the EQS, emissions need to be reduced. Because this legislation is not coupled to pharmaceutical legislation, the reduction of emissions currently can only be enforced via upgrading sewage treatment plants. This is not only very costly, but also requires energy (carbon footprint) and materials and thus is not always overall sustainable.

The gap between regulatory frameworks can only be bridged by legal changes. One option would be to make re-evaluation and subsequent risk mitigation mandatory if a risk has been identified in another (EU or national) legislative framework. Additionally, a database should be developed to transparently report relevant data to be used in other frameworks, and to flag APIs with a predicted risk so water managers know that special attention should be paid to these substances. This is all needed to install a good system to apply the correct risk mitigation (see goal 2 and accompanying paper (Moermond et al., 2023)).

2.4. Goal 4: The ERA is the same for similar products

According to the current legislation, an ERA with experimental data is required for each medicinal product. As a consequence, and in absence of a central database, new Applicants provide new dossiers with new studies, including vertebrate studies (on fish) when needed, for products with the same API of products already on the market. This requires resources to be spent by Applicants and assessors without any improvement for environmental protection. Furthermore, it is against the principle of 3Rs and counteracts harmonised assessments between products. For veterinary pharmaceuticals, it was shown that slightly different environmental fate and effects data are used in MA applications for similar products (i.e., products with the same API, same therapeutic indication, same pharmaceutical form and same dosing). As a consequence, the conclusions on environmental impact, the communication in the product information and risk mitigation measures may differ among products even though these products are interchangeable. There could be a serious lack of level playing field if product A with dossier A does not show a risk, and a similar product B with dossier B shows a risk and then has mandatory risk mitigation.

A solution to this would be to perform a substance-based assessment, with the same environmental fate and effects data used for each medicinal product containing the same API. This would lead to harmonised conclusions on the ERA and risk mitigation measures for similar products. A monograph system, like proposed for veterinary pharmaceuticals (de la Casa-Resino et al., 2021) and established in other regulatory frameworks (e.g., plant protection products and biocides) might also be useful for human pharmaceuticals.

Such a monograph system should serve as a central repository for quality-assessed environmental fate and effects data for all APIs, which may have to be re-assessed when testing protocols change or other relevant new information becomes available (see goal 3). In a long term, such ‘one access point’ on regulatory approved environmental data for human pharmaceuticals will lower administrative burdens, harmonize assessment results of similar products, and increase transparency towards stakeholders (Schwonbeck et al., 2021). Best practices from other regulatory frameworks with monograph systems should be used to

optimally design this system for human pharmaceuticals. In the EU, various chemical regulatory regimes (covering industrial chemicals, pesticides, feed additives, biocides and pharmaceuticals) are in place (Schwonbeck et al., 2021). The transparency regarding data related to use, fate and behaviour of substances and their environmental effects varies substantially, sometimes dependent on data protection (Tarazona et al., 2003; Oelkers, 2021a,b). While comprehensive and detailed ecotoxicological information is provided within some legislative frameworks (e.g., for biocides, pesticides and feed additives), relevant data related to environmental risk for pharmaceuticals is scarce, not easily accessible and often limited just to outcomes of the procedure (see section on data transparency). In future, a combined system for all substance frameworks should be envisaged to fully meet EU's one substance-one assessment goal.

2.5. Goal 5: ERA data are publicly available and easy to find by stakeholders

According to international and EU environmental information law (environmental information according to Art. 2 (3) (b) Aarhus Convention), there is in principle a right of access to environmental data such as the ERAs of pharmaceuticals. In practice this is ineffective due to product-based data and allegedly conflicting commercially/industrial confidential information (European Commission, 2019b; Oelkers and Floeter 2019; Oelkers, 2020, 2021b). As stated in goal 4, for APIs used in human medicinal products, no centralised and harmonised data repository is currently available. Environmental data related to human pharmaceuticals are published in the (E)PAR - (European) public assessment report of the authorised products, which can be found on the website of the EMA or National authorities. For stakeholders, it is not always clear where to start searching. Besides this, often the ERA data is not even taken up in the (E)PAR or consists of only a statement referring to a non-specified other product. In addition, there is no mechanism in place that assures that ERA data in (E)PARs are updated, e.g., after additional data are provided via post-marketing commitments or with new information from subsequent procedures for other, similar, products. As a result, obtaining substance-specific ERA data from these (E)PARs is often difficult, time consuming and with no guarantee for success.

To effectively protect humans and the environment from toxic chemicals, data on chemicals should be easily findable, accessible, interoperable and re-useable (FAIR) (Wilkinson et al., 2016). Availability of (environmental) data on chemicals is part of the EU Commission's Chemicals strategy (European Commission, 2020a), including a request for harmonisation of data ('one substance, one assessment', see goal 4). As such, quality assessed environmental effect and fate data on APIs on the EU Member States markets should be made publicly available in a publicly accessible database (Oelkers, 2020, 2021b).

Besides this, supporting legal mechanisms should be adopted to allow data sharing and data re-use not only between applicants but also between different EU Agencies and Member States. Publication of (meta)data will have to follow predefined criteria/protocols and data sharing should be governed by specific legal provisions. This way, environmental data may be available to all interested stakeholders, while study reports remain confidential and owned by the individual industries. Different levels of access may exist for e. g. regulatory authorities, academic researchers or members of industry consortia. A well-defined database will assist stakeholders when searching for and retrieving substance-specific information, which is needed to support environmental risk management.

2.6. Goal 6: Environmental data for legacy products without an ERA are generated via a catching-up procedure

As stated in the introduction, environmental data is lacking for a remarkable number of medicinal products, covering more than the half of APIs present on the German market in predicted concentrations where environmental risks might arise (Gildemeister et al., 2022). These are APIs in legacy products that were authorised before 2006 and for which an ERA has never been performed, or in generic products that can refer to these legacy products. Many of these products are used by a large population, which may lead to substantial emissions of their APIs and subsequently also to risks to the environment. A catching-up procedure to obtain environmental data for these APIs will enable potential environmental risks for medicinal products to be identified and managed accordingly.

To establish such a catching-up procedure, a new legal provision in the human medicinal products legislation is needed. However, the generation of new environmental data should not lead to delays in current authorisation procedures of generics, which would be inconsistent with the goal of the pharmaceutical strategy to accelerate procedures and increase availability of medicines to patients. Thus, a prioritisation approach is needed to decide which API in legacy products should be tested first independently of new applications. A number of prioritisation schemes, using different types of data, have been proposed e. g. (Huggett et al., 2003; Besse and Garric 2008; Cooper et al., 2008; Muñoz et al., 2008; Fick et al., 2010; Perazzolo et al., 2010; Berninger et al., 2016; Bu et al., 2020; Jameel et al., 2020; Gildemeister et al., 2022). Comparison of such schemes has shown that the outcome varies considerably depending on the data on which the scheme is based (Roos et al., 2012; Letsinger and Kay 2019). The possibility to obtain a good overview of available ERA data is crucial to prevent unnecessary testing of APIs and to identify APIs for which an ERA is not available. The development of a substance-based monograph system, in combination with provisions on sharing of data between Applicants, will lead to the most efficient time and resource investments. Following the e-ERA proposal, consortia of MA holders for the same API should be established, who then provide a joint ERA. This ERA can be filled first with data from the public domain, if reliable and relevant according to set standards (Moermond et al., 2016). For substances with incomplete data, experimental studies will then have to be provided.

Currently, within the PREMIER (Prioritisation and Risk Evaluation of Medicines in the EnviRonment) project prioritisation schemes are further elaborated, and an ERA will be provided for 25 API before mid 2026 (https://imi-premier.eu/). The European Commission still needs to decide whether this can serve as starting point for a regulatory catching–up procedure.

When a risk is identified, the monograph system could also be used to identify all products with similar exposure profiles. Legal provisions should then allow for these products to be harmonised regarding risk communication and mitigation measures.

In Regulation (EU) 2019/6 on Veterinary Medicinal Products, MA applications for generic products are exempted from providing an ERA when the MA for the reference product was granted before October 1, 2005 (Art. 18 (7)). Following a similar approach for generics in the new human pharmaceuticals legislation means that many of these products will continue to lack an ERA and an adequate risk mitigation because there are no data available for the reference products. Such an approach as stand-alone solution to accelerate procedures of generic applications means less environmental protection. Therefore, it needs to be combined with a catching-up procedure to facilitate efficient procedures while ensuring environmental safety.

2.7. Outlook

As the new pharmaceutical legislation may be in place for the next decades, it is important that the requirements in this legislation ensure efficacy and safety for the patient as well as safety for the environment and human health (via the environment). This needs careful considerations of protection goals in the environmental risk assessment and subsequent risk mitigation. In this paper, we discuss six main recommendations. The backbone is that environmental risks should be made

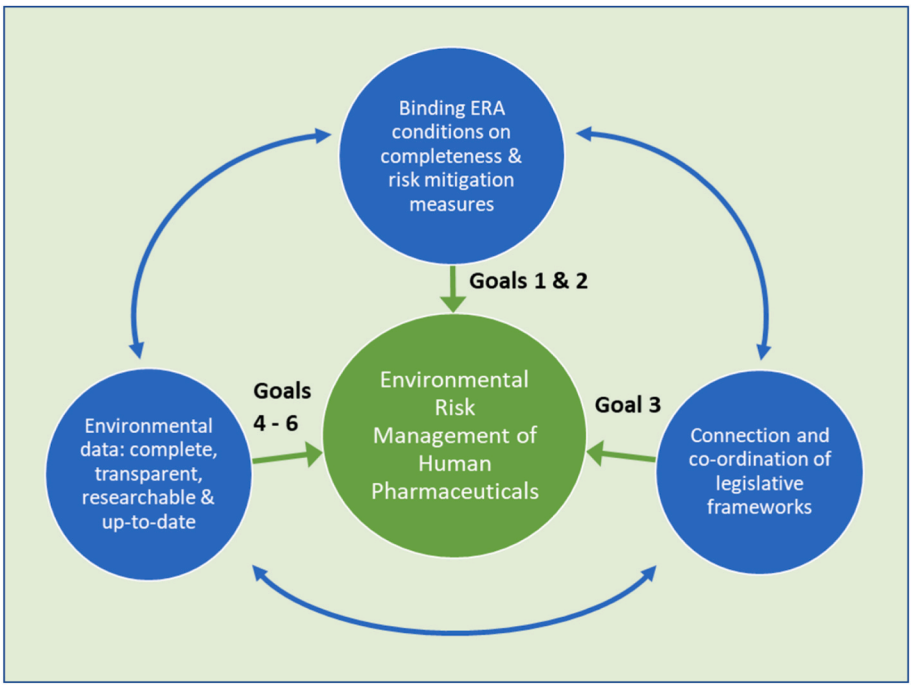

Fig. 3. Comprehensive system for an effective environmental risk management based on changes in the EU pharmaceuticals legislation.

transparent and mitigated as far as possible on the basis of sound and complete ERA. In conjunction with the strategy for risk mitigation (Moermond et al., 2023) this ensures a comprehensive environmental risk management (see Fig. 3).

The proposals in this paper are in line with the aims of the European Commission's one substance/one assessment approach, the Green Deal, and the Zero Pollution Ambition (European Commission, 2019a, 2020a, 2021c)).

We acknowledge that introducing changes in the current system may lead to temporary higher burdens for industry as well as regulators. However, in the long term we anticipate that the proposed approaches will lead to accelerated procedures, also regarding environmental safety. More importantly, having a balanced and effective interaction between marketing authorisation and environmental legislation will lead to a higher level of protection for both human and environmental health.

Disclaimer

The views expressed in this paper are the views of the authors only, and not necessarily of their institutions/Member States.

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CRediT authorship contribution statement

Daniela Gildemeister: Conceptualization, Data curation, Writing – original draft, Visualization, Supervision. **Caroline T.A. Moermond:** Conceptualization, Writing – original draft, Supervision. **Cecilia Berg:** Writing – original draft. **Ulrika Bergstrom:** Writing – original draft. **Lucie Bielská:** Writing – original draft. **Maria Grazia Evandri:** Writing – original draft. **Marco Franceschin:** Writing – original draft. **Boris Kolar:** Writing – original draft. **Mark H.M.M. Montforts:** Writing – original draft. **Christine Vaculik:** Writing – original draft, Investigation, Writing – review & editing.

Declaration of competing interest

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Data availability

The data that has been used is confidential.

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