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Proposal for regulatory risk mitigation measures for human pharmaceutical residues in the environment

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ABSTRACT

Environmental risks of human pharmaceutical products should be made transparent and mitigated as far as possible. We propose to apply a risk mitigation scheme to the marketing authorisation of human medicinal products which is pragmatic and tailored, and thus will not increase the burden to regulators and industry too much. This scheme takes into account increasing knowledge and accuracy of the environmental risk estimates, applying preliminary risk mitigation when risks are determined based on model estimates, and definitive, more strict and far-reaching risk mitigation when risks are based on actual measured environmental concentrations. Risk mitigation measures should be designed to be effective, proportional, easy to implement, and in line with current (other) legislation, as well as not being a burden to the patient/health care professionals. Furthermore, individual risk mitigation measures are proposed for products showing environmental risks, while general risk mitigation measures can be applied to all products to reduce the overall burden of pharmaceuticals in the environment. In order to effectively mitigate risk, linking marketing authorisation legislation to environmental legislation is essential.

1. Introduction

In each phase of a medicinal product's lifecycle, pharmaceutical residues may be released into water systems: from the manufacturing of the active pharmaceutical ingredients (API), via the patients' use and subsequent wastewater treatment, to the incorrect disposal of expired, unused, or leftover medicinal products via the sink or toilet. Although the primary aim of human pharmaceuticals is to protect human health (in terms of diagnosis, prevention, and treatment of diseases), their use and subsequent emission into the environment may in turn lead to negative effects on ecosystems and human health (e.g., via drinking water), as human and environmental health are intrinsically linked (one-Health; [CDC, 2022]). Pharmaceutical residues are generally not fully removed in sewage treatment plants (STPs) and are discharged into surface waters. They have been frequently detected in surface waters (like rivers) worldwide [Aus der Beek et al., 2016; Wilkinson et al., 2022], even at concentrations that (potentially) impact aquatic ecosystems and drinking water resources [World Health Organization, 2017]. Environmental risks to wildlife are mainly due to sub-lethal effects that can impact both individual fitness and population health. Examples include histopathological changes to tissues, feminisation of male fish and behavioural changes in both fish and aquatic invertebrates [Kidd et al., 2007; Tyler and Goodhead, 2010; Miller et al., 2018; OECD, 2019]. The presence of pharmaceutical residues (antibiotics) may also

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accelerate development of antimicrobial resistance due to bacterial selection pressure [Kotwani et al., 2021].

The presence of pharmaceutical residues in the environment is raising societal concerns world-wide [Damania et al., 2019; OECD, 2019]. Within the EU Water Framework Directive (EU Directive, 2000/60/EC), several pharmaceuticals were placed on a so-called Watchlist in 2015, and some of these are now flagged as potential priority substances for water quality [European Commission, 2022a]. The European Commission commissioned a report on the scale of the problem [BIO Intelligence Service, 2013] and has published a strategy on pharmaceuticals in the environment [European Union, 2019]. As a result, environmental issues are one of the main themes of the upcoming revision of the EU Pharmaceutical legislation (current EU Directive 2001/83/EC and Regulation (EC) No 726/2004) [European Commission, 2020a; European Commission, 2023]. It should be noted that this paper was written before the draft Pharmaceutical legislation was published and therefore no direct link between the proposals in this paper and the provisions in the draft legislation is made.

Regarding the marketing authorization (MA) procedure of medicinal products for human use, article 8.3 of the current EU Directive 2001/83/EC states that "… 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." Besides this, the Product Information for the medicinal product should contain "… reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.".

However, the impact on the environment is explicitly excluded from the benefit/risk (B/R) balance in accordance with Art. 26(1)(a) and Art. 1(28)(a) of this Directive, which means that when a risk to the environment is predicted in the Environmental Risk Assessment (ERA), this is not a reason to refuse MA nor to apply mandatory risk mitigation. In practice, once a medicinal product is approved, the safety measures for controlling its environmental impact are mostly limited to generic guidance sentences on waste disposal in the Product Information. These statements are not mandatory and of limited relevance for environment protection. Thus, there are currently no mandatory requirements for risk mitigation measures (RMMs) when the ERA is concluded with a risk to the environment, nor for post-approval monitoring of emissions of pharmaceuticals into the environment, e.g., by reporting consumption data in the Member States or monitoring environmental concentrations of substances of concern.

For the up-coming revision of the EU pharmaceuticals legislation (current EU Directive 2001/83/EC and Regulation (EC) No 726/2004) amendments of the ERA are suggested in an accompanying paper [Gildemeister et al., 2023]. In relation to these, there is a need for RMMs, which we propose to be mandatory when a (potential) risk of a pharmaceutical product to the environment is identified. Several legislative and non-legislative measures have already been identified [BIO Intelligence Service, 2013; European Union, 2019; OECD, 2019]. However, no guidance is in place yet as to when risk mitigation should be applied and which measures are suitable from a patient and an environmental perspective. For veterinary pharmaceuticals, RMMs are a more integral and binding part of MA, as the ERA outcome regarding environmental risk is part of their B/R assessment. The Reflection paper on risk mitigation measures for veterinary pharmaceuticals [European Medicines Agency, 2012] states that "risk mitigation is an essential part of the evaluation of products; risk mitigation can be used to restrict the risk associated with a product to an acceptable level, or even to completely remove such a risk. In principle, the applicant should propose RMMs and, if appropriate, the efficacy of such measures should be substantiated by data in the dossier. "

Thus, although an ERA is performed for the MA of human pharmaceuticals in the EU, an identified risk does not lead to RMMs for the specific API or medicinal product. The current paper is written as a discussion starter by a group of regulatory risk assessors of whom some have over 15 years of experience, and is accompanied by a paper that discusses other proposals to strengthen the regulatory ERA in the new EU general pharmaceuticals legislation [Gildemeister et al., 2023]. The aims of the current paper are (1) to identify factors that risk mitigation options for human medicinal products should comply with, (2) to propose a stepwise procedural framework, and (3) to identify examples of risk mitigation options for human medicinal products.

The ERA for human medicinal products (Fig. 1) includes a hazard assessment and a risk assessment (where risks are determined as a resultant of expected use and predicted ecotoxicological effects). The hazard assessment concerns intrinsic hazardous properties of a molecule, like persistence, bioaccumulation and toxicity (PBT), regardless of its environmental exposure [Moermond et al., 2012; European Chemicals Agency, 2022]. PBT substances (like PFOS – perfluorooctane sulfonic acid; and dioxins) are undesired in the environment regardless of their exposure. When an API meets all three PBT criteria and thus is a hazard, all possible measures should be taken to avoid emissions of this substance into the environment. In contrast, for other APIs with an identified risk, mitigation measures may be more tailored. In the present paper (as well as in the authorisation procedure) the ERA relates to both hazard and risk, but our proposed scheme refers to risk-based approaches. By APIs, we mean the substances in the product that exert a biological effect, as well as any toxicologically relevant metabolites of these substances that are excreted.

2. Risk mitigation of pharmaceuticals: Aim and boundary conditions

Risk mitigation may be needed in all phases of a medicinal product's lifecycle (from manufacturing, via use in patients, to handling of disposed products and water treatment) and may be generally applicable to all pharmaceutical products or targeted towards specific pharmaceuticals for which a risk is identified. It may include short-term solutions (e.g., limited advertising) as well as long-term measures (e.g., development of more sustainable APIs [Moermond et al., 2022]). Many general measures can be applied, regardless of whether APIs pose an environmental risk or not, which do not need changes in EU legislative frameworks. Such general risk mitigation options are discussed briefly in section 4. The remainder of this chapter and chapter 3 will focus on specific risk mitigation for APIs or medicinal products for which an environmental risk is identified, either via the ERA or via other regulatory frameworks.

The overall aim of risk mitigation is that the impact of pharmaceuticals in the environment should be reduced. RMMs can be designed to reduce emissions into the environment in a direct way (e.g., by reducing emissions due to the use of urine bags for a specific API) or indirectly (e.g., by communicating about risk and thus increasing awareness, leading to a conscious use and disposal of medicinal products).

For veterinary pharmaceuticals for which a risk is identified in the ERA, some general conditions for RMMs were described in the reflection paper [European Medicines Agency, 2012] as well as by Liebig et al., [2014]. Some of the principles behind these ideas also apply to human pharmaceuticals. To start with, for human medicinal products, the most important condition should be that the patient always comes first, and should be treated with safe and effective therapies. Physicians should keep their freedom for selection of the most appropriate medical treatment available in the current healthcare systems. Measures should address a problem (identified risk to the environment), they should be proportionate, and should be in line with relevant (other) laws (be legitimate). Liebig et al., [2014] state that it should be possible to monitor compliance with these measures and to give penalties if not complied with, although it is unclear who should receive those penalties. To be able to enforce risk mitigation, a first step is to make the ERA and associated RMMs mandatory. Here it should be carefully

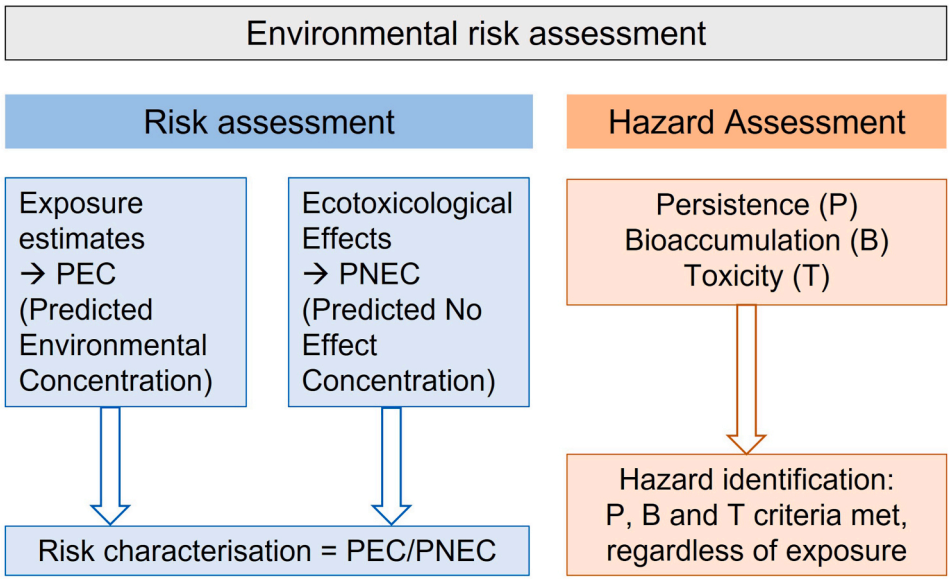

Fig. 1. General environmental risk assessment (ERA) scheme according to the guideline for the marketing authorisation procedure [European Medicines Agency, 2006]. The ERA includes both a risk assessment and a hazard assessment based on the criteria given under REACH [European Chemicals Agency, 2017].

considered who is addressed (health care professional, patient, down-stream actors) and what legally can be required [Montforts et al., 2004]. One important aspect stated in Liebig et al., [2014] and Montforts et al., [2004] is that the action should be verifiable, e.g., by means of re-assessment of the exposure. Analogous to what is stated in the reflection paper for veterinary pharmaceuticals, it should be possible for human health care professionals and patients to incorporate RMMs in daily practice to ensure compliance.

In the subsequent sections, we propose a scheme which adds risk mitigation to the ERA. This scheme consists of several steps, where increasing accuracy of the risk prediction and measurement goes hand in hand with the extent of risk mitigation proposed, moving from preliminary to definitive RMMs. In the scheme, the attention also moves from a product-based assessment, following the current regulatory ERA [European Medicines Agency, 2006], to API-based risk mitigation at the end.

3. Risk mitigation scheme

3.1. Step-wise approach

In our scheme (Fig. 2), there are three starting points to trigger (re-) assessment of the ERA and subsequent risk mitigation. Each starting point leads to different steps in the procedure. This scheme applies to risks due to the use of human medicinal products.

- **Starting point 1** is the point where the ERA is performed for a medicinal product at MA. Here, a risk is estimated based on emission estimates on the one hand and ecotoxicological effect data on the other hand, according to the EMA ERA guideline [European Medicines Agency, 2006]. The emission estimates are realistic worst-case, either based on a default value (1% of a population uses a certain product every day) or refined based on prevalence of the indication, metabolism, and/or sewage treatment efficiency. When an API is authorized for the first time, it normally takes some years for it to be fully established on the market and thus, an environmental risk will not become apparent in the short term. Consequently, for a new API with an identified environmental risk it is sufficient to apply easy-to-implement risk management (e.g., using tissues to wipe off access creme or gel), observe how consumption of the product actually develops and to re-assess the ERA after a certain amount of time. When re-assessment shows that this actual consumption could lead to a risk, further measures should be taken and actual monitoring should be performed in the environment.
- **Starting point 2** is where concerns arise from new information, i.e. consumption data for products that have already been on the market for some time or new knowledge on ecotoxicity. The information on consumption data is primarily of importance for APIs which have been authorized before the risk mitigation scheme has been put in place, for which a risk may have been predicted in the original procedure, and for which no RMMs have been designed yet. Another reason to enter the scheme here, is new information on ecotoxicity which could lead to a lower Predicted No Effect Concentration (PNEC; see Fig. 1), and thus a higher risk. APIs in products that were authorised before 2006 and for which no ERA is available (legacy APIs) should be prioritized for assessment of environmental risks [Gildemeister et al., 2023] and may enter the scheme also in step 2, with an ERA based on actual consumption data.
- **Starting point 3** concerns those APIs where risks are identified in environmental compartments. This could also happen within other legislative frameworks, e.g. the priority substances list under the Water Framework Directive, for which the European Commission has recently proposed to include a number of APIs [European Commission, 2022a]. This inclusion is based on water monitoring results throughout Europe and Environmental Quality Standards (EQS; comparable to a PNEC) which are derived using data from peer-reviewed literature.

Within this stepwise approach, the possibility of re-evaluation of the ERA in a regulatory context is a central theme. This re-evaluation should be performed regularly for APIs of concern (every 5 years when the PEC/PNEC is above 0.1). For the other APIs, re-evaluation is only needed when new information would lead to a different outcome of the risk assessment (e.g., at Start 3), and should be initiated by Member States or the European Medicines Agency (EMA). Following the industry's eERA proposal [European Federation of Pharmaceutical Industries and Associations, 2016)], after patent expiry the ERA should also be updated with new information, so generic products can enter the market with up-to-date environmental data. Re-evaluation can also be used to show that RMMs have been effective or are still needed.

The risk mitigation applied according to this scheme becomes more strict and far-reaching when the evidence on risk increases. When a risk

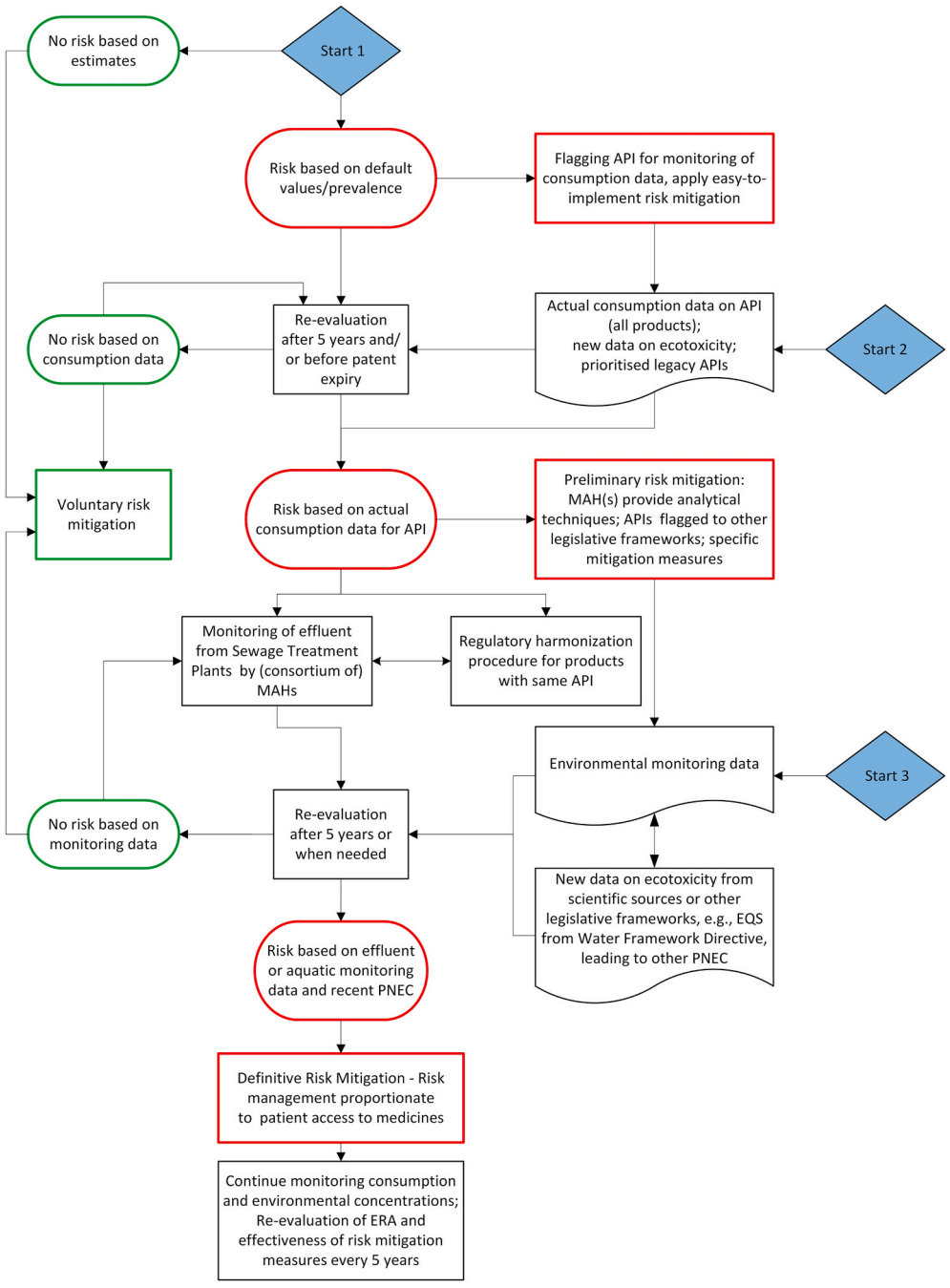

Fig. 2. Scheme for (re-)assessment of the environmental risks of human pharmaceuticals and subsequent risk mitigation measures. API: active pharmaceutical ingredient, MAH: market authorisation holder, ERA: environmental risk assessment, PNEC: predicted no effect concentration, EQS: environmental quality standard.

is identified in the ERA based on default values (upper part of the figure), substances should be flagged for further action e. g., monitoring of consumption data. Based on this, when a risk is identified, preliminary risk mitigation should be applied. This includes flagging the API as a possible compound of concern, including provision of analytical techniques for relevant environmental matrices by the applicant. This information should be part of a public database with environmental data, so it can be accessed by all relevant stakeholders (see also [Gildemeister et al., 2023]). At the same time, preliminary RMMs should ensure that the product will become available for patients that need it, but that e.g., it will not be sold over the counter and advertising is limited. Which risk mitigation measures (see Chapter 3.3) are applied depends on the product and has to be decided by regulatory experts based on proposals by the MAH in the ERA dossier. Besides this, risk mitigation should be harmonized between products with the same active ingredients, which may have to be enforced via a so-called referral procedure for products already authorised.

3.2. General considerations on the step-wise approach

When the scheme moves from predictions to actual measurements via monitoring in water, it also moves from a product-based assessment to an API-based assessment. To ensure that the same RMMa are applied to all products with the same API and similar use profiles, it will be necessary to perform regulatory harmonisation procedures. To facilitate this process, a substance-based ERA framework would be much preferred above the current product-based ERAs [Gildemeister et al., 2023] and as also proposed for veterinary pharmaceuticals [De la

Case-Resino, 2021; Schwonbeck et al., 2021].

The scheme in Fig. 2 has been designed for surface water, with monitoring in sewage treatment plant effluent after a risk is identified based on consumption data, because this is the environmental compartment where human pharmaceutical residues usually enter the environment. However, the ERA for human medicinal products also includes an assessment of risks to groundwater, soil and sediments. The scheme may also be applied to these compartments, using monitoring data from these compartments and/or relevant other environmental legislative frameworks.

When the results of the ERA shows that monitoring in environmental compartments becomes necessary, the marketing authorisation holders (MAHs) should propose a monitoring scheme as part of the ERA dossier and subsequently, be responsible for performing environmental monitoring. APIs should be monitored at locations where the risks are estimated to be relatively high (urban areas, high consumption) and where other sources like production locations can be excluded. Monitoring should be performed at different locations and seasons, and at conventional sewage treatment plants without additional treatment like ozonation, UV treatment, and activated carbon. Monitoring in effluent is preferred above monitoring in the receiving surface water, because the dilution from effluent to surface water can vary from almost none to a factor of >100.000 [Link et al., 2017]. How to setup monitoring and compare monitoring data to the PNEC should be further detailed in a specific guidance document.

Monitoring of an API provides information on its occurrence in the environment, but does not make any distinction between the possible sources of the API. Thus, when monitoring concentrations show a risk, the evaluation of the risk and subsequent risk mitigation should also take into account whether there are other uses that could have caused emissions of this API, such as production locations, veterinary pharmaceutical, biocides, or production locations. For effective environmental management, monitoring data should also be part of a substance-based database.

3.3. Defining specific risk mitigation measures for APIs with a risk

After the identification of an environmental risk for an API or medicinal product, preliminary or definitive RMMs should be defined, according to the boundary conditions described in section 2. When designing specific RMMs, it is important to take into account that they are legitimate, lead to reduction of risk, be proportional, be in line with current (other) legislation easy to implement, and they should not burden the patient too much. These boundary conditions, as discussed in section 2, and risk mitigation possibilities should be further elaborated on in a guidance document, also including the monitoring aspects mentioned in section 3.2. An example of such a guidance document is already in use for veterinary medicinal products [European Medicines Agency, 2012]. As explained in section 3.1, when a risk is identified, the first step is to flag the API as a possible compound of concern, including provision of analytical techniques. Monitoring and re-evaluation of the ERA are always an integral part of risk mitigation when the ERA ends with a (calculated) risk.

RMMs should always take into account the intended use, which may be very product-specific. Thus, for products with the same API but different indications/applications, it may be necessary to apply different RMMs. It should also be kept in mind that there may be a (financial) cost for risk mitigation, while on the other hand not applying risk mitigation will place the costs on water treatment. Besides this, pharmaceutical companies may benefit from a reputational perspective by enhancing their "green" credentials and investing in more environmentally friendly pharmaceuticals [Moermond et al., 2022].

Some examples of specific mitigation options are:

- ***Restricting use to prescription-only.*** Medicines should only be used when needed, but self-medication may increase the amount of API used and thus emissions into the environment [OECD 2019; Tscharke et al., 2022]. Thus, over the counter availability of drugs may not be preferred from an environmental risk point of view.
- ***Appropriate prescription/dispensing rules.*** Prescribing or dispensing the exact amount of the product that the patient needs, reduces the amount of leftover medication. For products with a risk, preventing leftover medication is especially important as this also reduces the amount thrown away, possibly erroneously via the sink or toilet. Treatment initiation packs may contain smaller amounts of different dosages which can be used to determine the adequate, optimal, dose for the patient.
- ***Optimising administration routes.*** Environmental impact may depend on the route of administration, e.g., injection, oral or topical. Some of these may have a lower environmental impact while effectiveness to the patient is still the same or even better, others may have a lower environmental impact but may have more side-effects. It is acknowledged that the choice of the route of administration takes different aspects into consideration that should be evaluated carefully even including the environmental impact. Precise dosing systems may be another option, as well as personalized diagnostics to evaluate the appropriate dose for an individual patient.
- ***Restricting advertising.*** Advertising is described in current legislation (EU Directive, 2001/83 art. 86) as "any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products …". To avoid unnecessary use of an API, advertising for its products should be restricted when it poses an environmental risk. This is mainly important for products that are available over the counter, where advertising is directed towards patients. However, also advertising towards physicians for prescription-only products should be limited. Advertising restrictions need to be proportionate, and in case advertising would be allowed, it should also contain information about the environmental risks.
- ***Prevention of wash-off.*** Wash-off of creams and gels may be prevented by different RMMs, like advising patients not to shower shortly after application and to use a paper towel before washing hands after administration [Bielfeldt et al., 2022]. This may reduce topical diclofenac in rinse water up to 70%. However, effectiveness with regards to patient compliance and total emissions should still be demonstrated.
- ***Collection of patient's excreta e.g., urine bags.*** When use of a pharmaceutical is necessary, under some circumstances patient's excreta may be collected. In the Netherlands, a pilot project with urine bags to collect X-ray contrast media has shown that patients are very willing to use them [Moermond and de Rooy, 2022]. Also in Germany pilot projects demonstrated the feasibility and effectiveness of such measures [Merk'Mal, 2022]. In both countries, further larger projects are being planned. In some cases however, the use of urine bags may bother patients too much, e.g., when patients with cancer would have to collect their urine with chemostatics. In this case, the patient's benefit outweighs environmental benefits (which are limited in practice, based on actual use data [Moermond et al., 2018]). When the use of urine bags or other collection systems is a good risk mitigation option, MAHs may be obliged to provide these with their treatment.
- ***Evaluation of alternative medicinal or non-medicinal treatments.*** Normally, every medicinal product is assessed for its own benefit/risks. However, in case of an environmental risk, alternatives may be assessed and prioritized for environmental risks. This should then be part of communication material for doctors and patients, helping them to make choices that are good for the patient as well as the environment.

4. General risk mitigation measures

Although the number of APIs that individually pose a risk to the

environment is likely to be limited, all pharmaceuticals emitted into the environment may contribute to a risk, e.g., because of mixture toxicity [Backhaus, 2014]. This warrants taking mitigation measures on a general level, to reduce overall emissions of pharmaceuticals into the environment. Besides this, many of the general RMMs to reduce emissions also impact the amount of pharmaceutical ingredients that is not used and hence will not need to be produced, packaged and distributed, which is another sustainability aspect [Smale et al., 2021].

Several general RMMs have been published by the European Commission (e.g., in their Strategic Approach on Pharmaceuticals in the Environment [2019]) and the underlying BIO Intelligence Service report [2013], by the OECD [2019], and recently by Helwig et al., [2023]. Many general RMMs may be part of larger overall approaches, like the Dutch Chain Approach on Pharmaceuticals [Moermond and de Rooy, 2022] and the German approach [BfArM and UBA 2017], the Spanish SIGRE system [SIGRE, 2022] or Extended Producer Responsibility Schemes. Examples of general RMMs are:

- ***Improved diagnostics, prescription, and non-clinical interventions.*** As stated by the OECD [2019], over-prescription, self-medication (over-the-counter pharmaceuticals) and misdiagnosis of symptoms can increase the amount of pharmaceutical residues in the environment. Improving diagnostics may also lead to more targeted treatment of the disease. A yearly evaluation may prevent overconsumption due to polypharmacy and non-clinical interventions like psychological therapy instead of taking antidepressants also help to reduce emissions.
- ***Responsible use of medicines, awareness.*** Pharmaceuticals should only be taken when needed, with the right doses and for the correct indication. Awareness campaigns and use guidelines may help to increase prudent and responsible use of pharmaceuticals, for products available via prescription as well as over the counter.
- ***Reduce pack sizes and the amount distributed to patients.*** Sometimes, patients will get medication for a year even when they don't need it that long. As a result of dispensing unnecessary doses, spillage of unused medicines occurs with vast amounts of left-over medication as a result.
- ***Re-evaluation of expiry dates.*** Shelf-life of medication should be optimal for quality, but it should not be shorter than necessary. When products expire too fast, this increases the amount of waste in the distribution chain, and subsequently its environmental impact. Safely extending the "use-by" dates of medicines, based on prolonged stability studies, should be part of a re-evaluation procedure between MAHs and authorities.
- ***Collection of waste.*** Pharmaceutical waste should never be disposed of via the toilet or sink. Waste disposal and management systems for unused or expired medicinal products are in place in all EU Member States (Directive, 2001/83 art. 127b). In some Member States, the authorities arrange pharmaceutical waste collection, in others (e.g., France, Spain) extended produce responsibility schemes are applied and the pharmaceutical producers are made responsible. Adoption of best practices and harmonisation of collection and management systems across the EU are encouraged [Mitkidis et al., 2021]. It is important to provide adequate information to patients and healthcare professionals on correct disposal of all pharmaceuticals, not just those with a risk.
- ***Redispensing of unused pharmaceuticals.*** In the Netherlands, a research project has shown the feasibility of re-dispensing unused pharmaceuticals, in the first instance in hospital settings [Smale et al., 2021]. In Italy, besides a national no-profit organisation which collects unused, still valid medicinal products [https://www.bancofarmaceutico.org/], some regions have drafted guidelines on re-use of still valid, unused and correctly stored medicinal products coming from patients dismissed by long-term care facilities or by home therapies [Italian Law, 2011].
- ***Upgrading sewage treatment plants.*** An option to remove pharmaceuticals and other micropollutants is to upgrade all sewage treatment plants, as proposed recently by the EU Commission [European Commission, 2022b]. This will however be a long-term solution and is not only costly in terms of finances but also in terms of energy and material use.

5. Discussion and conclusions

The number of APIs with established risks to the environment is expected to be low [Gunnarsson et al., 2019]. Thus, it should be possible to deal with environmental risks of this limited number of pharmaceuticals and design and apply appropriate RMMs. In chapter 1, we briefly mentioned that APIs that meet PBT criteria and thus are a hazard regardless of the environmental exposure, should be prevented from entering the environment whenever possible. For this specific set of APIs, which is expected to be very small [Konradi et al., 2017; Constantine et al., 2020], all possible mitigation measures should be applied at time of authorisation or with the upcoming information about the hazard characteristics.

Linking environmental and MA frameworks is very important, as environmental information from MA is needed by water managers to assess water quality, and information from environmental frameworks could vice versa lead to mandatory RMMs [Gildemeister et al., 2023]. For APIs for which a risk is shown, e.g., within the Water Framework Directive, RMMs could be very important to reduce concentrations in the environment without the need to upgrade every sewage treatment plant. There may be cases where the EQSs derived within the Water Framework Directive or new PNECs are lower than the value used in the original MA dossier, because of new knowledge from peer-reviewed literature. This calls for a regular re-evaluation of ERAs, leading to more accurate risk estimates. When EQSs and PNECs are harmonized, this also leads to more harmonized assessments across frameworks, in line with the EU Commission's One Substance - One Assessment approach [European Commission, 2020b].

In an accompanying paper [Gildemeister et al., 2023] a number of aspects that should be part of the new pharmaceutical legislation are described. Many of these aspects are also important to design and implement appropriate RMMs, like the ERA being a mandatory part of the MA dossier, linking environmental and MA legal frameworks, a catching-up procedure for APIs without an ERA, a public database with environmental data and risk statements, and harmonisation of ERAs for APIs towards a substance-based assessment. The procedure for mandatory risk mitigation and re-evaluation should also be part of the revision of legislation.

Implementation of some of the proposed RMMs will not only be beneficial for water quality, but sometimes also for patients by reducing unnecessary medication. It may also impact overall sustainability, as explained in section 4. On the other hand, a measure that is beneficial for water quality (e.g., API that breaks down faster in the environment) may severely impact other sustainability aspects of the treatment, such as carbon footprint or material use (when it has to be transported in cooled systems). Although this paper focusses on risks of APIs after use, general sustainability criteria should also be considered when health care professionals and procurers make choices on which pharmaceutical to prescribe or buy. How to compare these sustainability aspects with each other and with safety, efficacy, pricing and availability aspects is part of an EU-funded research project on sustainable pharmacy (TransPharm; https://transforming-pharma.eu/).

Concludingly, environmental risks of human pharmaceutical products should be made transparent and mitigated as far as possible. This scheme takes into account increasing knowledge and accuracy of the environmental risk estimates, applying preliminary risk mitigation when risks are determined based on model estimates, and definitive, more strict and far-reaching risk mitigation when risks are based on actual measured environmental concentrations. Our scheme is

pragmatic and tailored, with RMMs and re-evaluation only needed for a limited number of APIs. As a result, it will not increase the burden to regulators and industry too much. In order to effectively mitigate risk, linking MA legislation to environmental legislation is essential.

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

Caroline T.A. Moermond: Conceptualization, Writing – original draft. **Cecilia Berg:** Writing – review & editing. **Ulrika Bergstrom:** Writing – review & editing. **Lucie Bielská:** Writing – review & editing. **Maria Grazia Evandri:** Writing – review & editing. **Marco Franceschin:** Writing – review & editing. **Daniela Gildemeister:** Conceptualization, Writing – original draft. **Mark H.M.M. Montforts:** Writing – review & editing.

Declaration of competing interest

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Data availability

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References

Aus der Beek, T., Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., et al., 2016. Pharmaceuticals in the environment-global occurrences and perspectives. Environ. Toxicol. Chem. 35 (4), 823–835. https://doi.org/10.1002/etc.3339.

Backhaus, T., 2014. Medicines, shaken and stirred: a critical review on the ecotoxicology of pharmaceutical mixtures. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1656) https://doi.org/10.1098/rstb.2013.0585.

Bielfeldt, S., Urquhart, D., Brandt, M., Hennighausen, N., Bazzanella, R., 2022. Reduction of residual topical diclofenac in waste water by a wiping procedure before hand washing. Chemosphere 292, 133350. https://doi.org/10.1016/j.chemosphere.2021.133350.

BIO Intelligence Service, 2013. Study on the environmental risks of medicinal products. In: Final Report Prepared for Executive Agency for Health and Consumers. https://ec.europa.eu/health/system/files/2016-11/study_environment_0.pdf.

Centers for diseases control and prevention (CDC), 2022. One health. https://www.cdc.gov/onehealth/index.html, 2022-12-14.

Constantine, L.A., Davidson, T., Häner, A., Hoeger, B., Maynard, S.K., Lee, M., Perkins, A. N., Ryan, J.J., Snape, J., Tell, J., Van Ginneken, I., Vestel, J., Wilson, P., Burden, N., 2020. Evaluation of the EMA Trigger for fish BCF Testing and secondary poisoning assessment: evaluation of LogD and fish BCF data for several pharmaceuticals. In: Poster at SETAC 2020 Conference.

Damania, R., Desbureaux, S., Rodella, A.-S., Russ, J., Zaveri, E., 2019. Quality Unknown: the Invisible Water Crisis. World Bank, Washington, DC. Available at: http://hdl.handle.net/10986/32245.

De la Casa-Resino, I., Haro Castuera, A., Casimiro Elena, R., Rubio Montejano, C., Carapeto García, R., 2021. European legislation for veterinary medicines: would a monograph system improve the environmental risk assessment? Integrated Environ. Assess. Manag. 17 (6), 1274–1285. https://doi.org/10.1002/ieam.4431.

European Chemicals Agency (ECHA), 2017. Chapter R11. Guidance on Information Requirements and Chemical Safety Assessment - ECHA (europa.Eu).

European Chemicals Agency (ECHA), 2022. PBT Assessment - ECHA (europa.Eu).

European Commission, 2020a. In: A Pharmaceutical Strategy for Europe. 25.11.2020 COM(2020) 761 Final. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761.

European Commission, 2020b. Chemicals strategy for sustainability. Towards a toxic-free environment. Available at: https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf.

European Commission, 2022a. Proposal for a directive amending the water framework directive, the groundwater directive and the environmental quality standards directive. In: Available at Proposal Amending Water Directives (europa.Eu).

European Commission, 2022b. Proposal for a Directive of the European Parliament and of the Council concerning urban wastewater treatment (recast). In: Available at Proposal for a Revised Urban Wastewater Treatment Directive (europa.Eu).

European Commission, 2023. Reform of the EU Pharmaceutical Legislation, 26 April 2023. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en.

European Federation of Pharmaceutical Industries and Associations (EFPIA), 2016. Eco-pharmacostewardship (EPS. Pillar 3 – Extended Environmental Risk Assessment (eERA). Available at: eps-pillar3-V3.cdr (efpia.eu).

European Medicines Agency (EMA), 2006. Guideline on the environmental risk assessment of medicinal products for human use. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf.

European Medicines Agency (EMA), 2012. Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products. EMA/CVMP/ERAWP/409328/2010. https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-risk-mitigation-measures-related-environmental-risk-assessment-veterinary-medicinal_en.pdf.

Gildemeister, D., Moermond, C., Berg, C., Bergstrom, U., Bielská, L., Evandri, M.G., Franceschin, M., Kolar, B., Montforts, M., Vaculik, C., 2023. Improving the regulatory environmental risk assessment of human pharmaceuticals: required changes in the new legislation. In: Article Accepted with Minor Revisions, Reference to Be Updated by Editorial Office.

Gunnarsson, L., Snape, J.R., Verbruggen, B., Owen, S.F., Kristiansson, E., Margiotta-Casaluci, L., Österlund, T., Hutchinson, K., Leverett, D., Marks, B., Tyler, C.R., 2019. Pharmacology beyond the patient – the environmental risks of human drugs. Environ. Int. 129, 320–332. https://doi.org/10.1016/j.envint.2019.04.075.

Helwig, K., Niemi, L., Stenuick, J.-Y., Alejandre, J.C., Pfleger, S., Roberts, J., Harrower, J., Nafo, I., Pahl, O., 2023. Broadening the perspective on reducing pharmaceutical residues in the environment. Environ. Toxicol. Chem. https://doi.org/10.1002/etc.5563 (in press).

Kidd, K.A., Blanchfield, P.J., Mills, K.H., Palace, V.P., Evans, R.E., Lazorchak, J.M., Flick, R.W., 2007. Collapse of a fish population after exposure to a synthetic estrogen. Proc. Natl. Acad. Sc.i U.S.A. 104 (21), 8897–8901. https://doi.org/10.1073/pnas.0609568104.

Konradi, S., Speichert, G., Wiemann, A., Schmitz, S., Prutz, I., Schönfeld, J., 2017. Hazard Assessment of Human Pharmaceuticals – a Review of Regulatory Data on Persistence, Bioaccumulation, and Toxicity Focusing on Halogenated Compounds (Poster at SETAC conference).

Kotwani, A., Joshi, J., Kaloni, D., 2021. Pharmaceutical effluent: a critical link in the interconnected ecosystem promoting antimicrobial resistance. Environ. Sci. Pollut. Res. Int. 28 (25), 32111–32124. https://doi.org/10.1007/s11356-021-14178-w.

Law, Italian, 2011. Italian Regional Law N. 23 of 11.11.2011. https://bur.regione.veneto.it/BurvServices/pubblica/DettaglioLegge.aspx?id=235945.

Liebig, M., Floeter, C., Hahn, T., Koch, W., Wenzel, A., Römbke, J., 2014. Risk mitigation measures: an important aspect of the environmental risk assessment of pharmaceuticals. Toxics 2 (1), 35–49. https://doi.org/10.3390/toxics2010035.

Link, M., Von der Ohe, P.C., Voss, K., Schäfer, R.B., 2017. Comparison of dilution factors for German wastewater treatment plant effluents in receiving streams to the fixed dilution factor from chemical risk assessment. Sci. Total Environ. 598, 805–813.

Merk'Mal, 2022. https://merkmal-ruhr.de. (Accessed 14 December 2022).

Miller, T.H., Bury, N.R., Owen, S.F., MacRae, J.I., Barron, L.P., 2018. A review of the pharmaceutical exposome in aquatic fauna. Environ. Pollut. 239, 129–146. https://doi.org/10.1016/j.envpol.2018.04.012.

Mitkidis, K., Obolevich, V., Chrysochou, P., Mitkidis, P., 2021. Harmonisation of pharmaceutical take-back systems in the EU. Eur. J. Health Law 28 (20 21), 445–471.

Moermond, C.T.A., de Rooy, M., 2022. The Dutch Chain approach on pharmaceuticals in water: stakeholders acting together to reduce the environmental impact of pharmaceuticals. Br. J. Clin. Pharmacol. 88 (12), 5074–5082. https://doi.org/10.1111/bcp.15509.

Moermond, C.T.A., Janssen, M.P.M., de Knecht, J.A., Montforts, M.H.M.M., Peijnenburg, W.J.G.M., Zweers, P.G.P.C., Sijm, D.T.H.M., 2012. PBT assessment using the revised annex XIII of REACH: a comparison with other regulatory

frameworks. Integrated Environ. Assess. Manag. 8 (2), 359–371. https://doi.org/10.1002/ieam.1248.

Moermond, C., Venhuis, B., van Elk, M., Oostlander, A., van Vlaardingen, P., Marinković, M., van Dijk, J., 2018. Cytostatics in Dutch surface water. Use, presence and risks to the aquatic environment. In: RIVM Letter Report 2018-0067. RIVM, Bilthoven, the Netherlands. Available at: Cytostatics in Dutch surface water (rivm.nl).

Moermond, C.T.A., Puhlmann, N., Brown, A.R., Owen, S.F., Ryan, J., Snape, J., Venhuis, B., Kümmerer, K., 2022. GREENER Pharmaceuticals for more sustainable healthcare. Environ. Sci. Technol. Lett. 9 (9), 699–705. https://doi.org/10.1021/acs.estlett.2c00446.

Montforts, M.H.M.M., Van Rijswick, H.F.M.W., Udo de Haes, H.A., 2004. Legal constraints on special precautions in EU product labelling to mitigate the environmental risk of veterinary medicines at use. Regul. Toxicol. Pharmacol. 40 (3), 327–335.

OECD, 2019. Pharmaceutical Residues in Freshwater, hazards and policy responses. In: OECD Studies on Water. OECD Publishing, Paris. https://doi.org/10.1787/c936f42d-en.

Schwonbeck, S., Breuer, F., Hahn, S., Brinkmann, C., Vosen, A., Radic, M., Vidaurre, R., Alt, J., Oelkers, K., Mezler, A., Floeter, C., 2021. Feasibility study of an active-substance-based review system ('monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products: final report, Publications Office of the European Union. 2021. In: Feasibility Study of an Active-Substance-Based Review System ('monographs') and Other Potential Alternatives for the Environmental Risk Assessment of Veterinary Medicinal Products : Final Report. Publications Office of the European Union. https://doi.org/10.2875/94477.

SIGRE, 2022. Medicamento Y Medio Ambiente. (Accessed 14 December 2022).

Smale, E.M., Egberts, T.C.G., Heerdink, E.R., van den Bemt, B.J.F., Bekker, C.L., 2021. Waste-minimising measures to achieve sustainable supply and use of medication. Sustainable Chemistry and Pharmacy 20, 100400. https://doi.org/10.1016/j.scp.2021.100400.

Tscharke, B.J., O'Brien, J.W., Ahmed, F., Nguyen, L., Ghetia, M., Chan, G., Thai, P., Gerber, C., Bade, R., Mueller, J., Thomas, K.V., White, J., Hall, W., 2022. A wastewater based evaluation of the effectiveness of codeine control measures in Australia. Addiction. https://doi.org/10.1111/add.16083.

Tyler, C.A., Goodhead, R.M., 2010. Impacts of Hormone Disrupting Chemicals on Wildlife Silent Summer: the State of Wildlife in Britain and Ireland. Cambridge University Press, pp. 125–140.

European Union, 2019. Communication from the commission to the European parliament, the council and the European economic and social committee of the European union strategic approach to pharmaceuticals in the environment, 11 march, 2019, COM(2019) 128 final. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52019DC0128.

Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., Leung, K.M.Y., Lai, R.W.S., Galbán-Malagón, C., et al., 2022. Pharmaceutical pollution of the world's rivers. Proc. Natl. Acad. Sc.i U.S.A. 119 (8), e2113947119 https://doi.org/10.1073/pnas.2113947119.

World Health Organization, 2017. Chemical mixtures in source water and drinking-water. Available at: https://apps.who.int/iris/handle/10665/255543.