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Recommendations for reducing adverse environmental impacts from human pharmaceuticals

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Improving environmental protection in EU pharmaceutical legislation

Recommendations for reducing adverse environmental impacts from human pharmaceuticals

by

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On behalf of the German Environment Agency

Executive Summary

Pharmaceutical residues in the environment are a rising health and environmental concern. [1] The number of pharmaceuticals detected in the environment is increasing endangering ecosystems.[2] Some active substances show effects on environmental organism at very low concentrations.[3] Antimicrobial resistances in the environment might threatens human's health.[4]

In 2020, the European Commission considered the need to better address environmental protection by raising the issue in the human pharmaceutical strategy[5]. Ensuring environmental sustainability and strengthening the environmental risk assessment are flagship initiatives of this strategy. The implementation of the strategic aims needs a revision of the general pharmaceutical legislation considering Directive 2001/83/EC and Regulation (EC) No 726/2004. This is a crucial opportunity to implement environmental improvements.

The German Environment Agency (UBA) is the competent authority for the environmental risk assessment (ERA) of human and veterinary medicinal products in Germany. We continuously improve knowledge about the occurrence and effects of pharmaceutical residues in the environment by means of research and data analysis. Based on this experience, we are convinced that far more efforts and legally binding regulations are needed to effectively reduce environmental impacts posed by human medicinal products. Various measures along the whole life cycle of medicinal products are necessary to reduce the environmental footprint of pharmaceuticals significantly:

► Strengthening the ERA and including mandatory risk mitigation measures in the authorisation procedure

The legal requirement of an environmental risk assessment (ERA) seemed to be a milestone towards better environmental protection. It promised a reliable set of data that being a precondition for targeted risk management. However, the experience of the last 17 years shows that measures are necessary to strengthen the ERA during the authorisation process as a comprehensive risk management cannot be enforced according to the current legislation. Therefore, ERA should be given the same relevance as other parts of the non-clinical safety assessment. The results of this risk assessment should be considered in the decision-making process during authorisation. In case environmental risks are identified, clear consequences such as post-market surveillance, prescription-only status and an advertising ban should be imposed. Including ERA in the pharmacovigilance part of the legislation would enable re-evaluations. Especially with regard to the One Health Action plan[6] , the main targets of the ERA should be clearly defined and environmental safety needs to be considered as an important component of health protection.

1 Gorka Orive, Unax Lertxundi, Tomas Brodin, Peter Manning; "Greening the pharmacy"; Science, 377 (6603), • DOI: 10.1126/science.abp9554

2 Wilkinson, J.L. et al.: Pharmaceutical pollution of the world's rivers. Proc Natl Acad Sci U S A 119(8) (2022). doi:10.1073/pnas.2113947119

3 Schwarz, S., Gildemeister, D., Hein, A., Schröder, P., Bachmann, J.: Environmental fate and effects assessment of human pharmaceuticals: lessons learnt from regulatory data. Environmental Sciences Europe 33(1), 68 (2021). doi:10.1186/s12302-021-00503-0

4 Larsson, D.G.J., Flach, C.-F.: Antibiotic resistance in the environment. Nature Reviews Microbiology 20(5), 257-269 (2022). doi:10.1038/s41579-021-00649-x

5 COM(2020) 761 final, 25.11.2020, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN

6 COM (2017): A European One Health Action Plan against Antimicrobial Resistance (AMR). https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf

► Closing data gaps and providing transparency of environmental information by establishing an active substance-based review system (monograph system)

Analyses of the provided data during authorization demonstrate that knowledge gaps on environmental fate and effects still exist. This is particularly worrying when it comes to substances with high volume consumption or for those found frequently in various environmental compartments. In order to close these knowledge gaps, a catching - up procedure for substances lacking environmental data (e. g. substances used in legacy products authorised before 2006) would be a suitable measure combined with compiling and publishing existing and newly generated data. The establishment of a monograph system together with provisions for data sharing, data availability, data storage and data update would be the next milestone towards better and sustainable protection of the environment. Furthermore, such a system can contribute to achieve the aims of the zero-pollution action plan of the EU[7] for the pharmaceutical sector including the 'one substance one assessment approach' as an important part of the EU chemical's strategy[8].

► Positioning of pharmaceutical legislation within other EU regulations and strategies

Risk mitigation measures that can be adopted as part of the approval process for individual medicinal products are currently insufficient to effectively minimize the entry of pharmaceutical residues into the environment and associated risks. Apparently, an effective implementation of risk mitigation measures can only be reached by the overlapping and coordinated addressing of the problem in different European legislations.[9] A clear connection is needed between environmental data required within the pharmaceutical's legislation and the use of these data for measures within other legislative frameworks for instance derivation of environmental quality standards. The EU Strategic approach to pharmaceuticals in the environment[10] proposes the consideration of pharmaceuticals in environmental legislative frameworks. Some of them are currently being revised or drafted (e. g. Urban Wastewater Directive, Soil Health Law) at the same time as the pharmaceutical legislation. So, this is the perfect moment to establish a coherent legislative framework. The foundation for the future interplay between the legislations should be defined in the pharmaceutical legislation.

► Making production more environmentally sustainable

Until now the focus on environmental impacts was related to the use of a medicinal product with its active substances. However, large environmental contamination at production sites has been reported, representing hotspots for the development and spreading of antimicrobial resistance. Those emissions pose a worldwide threat to human health that need to be tackled at a global level because active pharmaceutical substances are mainly manufactured in countries outside European. In consequence, transparency in terms of the supply chain is a requisite to control also environmental pollution during manufacturing. We propose the establishment of environmental manufacturing standards for products marketed in Europe. Such standards can include emission limit values which should be applied to all production sites. A straight way forward is to include environmental issues under the guidelines of good manufacturing practice. Inspectors should be legally enabled to control these standards. Compliance with emission limit

[7] COM (2021) 400; https://ec.europa.eu/environment/pdf/zero-pollution-action-plan/communication_en.pdf

[8] COM (2020) 667, https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf

[9] Umweltbundesamt, 2021: The Zero Pollution Action Plan as a chance for a cross-regulatory approach to pollution prevention and reduction | Umweltbundesamt

[10] COM (2019) 128 final

values should be declared in authorization procedures. This approach ensures a level playing field for producers inside and outside Europe.

We consider that the proposed amendments, i. e. strengthening ERA, setting clear actions for environmental safety, implementing catching-up procedure, establishing substance monographs, interlinking legislations and developing environmental standards for manufacturing, are measures for the protection of the environment and human health that clearly improve the current situation. UBA strongly supports the initiative of the EU to designate environmental challenges as one of the flagship actions in the general pharmaceutical legislation for human medicines and underlines the advantages of including pharmaceutical active substances in the one substance one assessment approach. The pharmaceutical legislation for human medicinal products would thus contribute to reducing environmental contamination with pharmaceuticals.

Content

1 Pharmaceuticals in the environment are a reason of particular concern

Residues of pharmaceutical active substances contaminate environmental resources for humans and might have negative impacts on environmental organisms. They might be found in all areas of the world.[11] Residues of pharmaceuticals were found in at least 89 countries in all UN regions. Main exposure sources are public waste water and industrial production sites. UBA has established a database[12] of published findings for pharmaceuticals in the environment all over the world. For Germany, 414 active substances or their transformation products were reported in different environmental compartments, 749 for the European Union and 992 worldwide. The number of detected substances in all compartments increased since 2015 (Table 1) globally and in the European Union of over 20%.

Table 1: Number of active substances including their metabolites or transformation products with detections in different environmental compartments

Number of	Global		European Union	
Year	**2021**	**Change to 2015**	**2021**	**Change to 2015**
detected substances	**992**	**+221**	**749**	**+153**
in WWTP[1] effluent/sewage/reclaimed water	771	+ 158	591	+117
in surface water/bank filtrate/groundwater/drinking and tap water	703	+ 175	483	+99
in manure/dung/sediment from aquaculture/SPM/biosolids/sludge	337	+192	250	+166
in sediment/soil/SPM	295	+111	227	+95

Source: UBA Pharms Database version 2 (2015) & version 3 (2021)

[1] Waste Water Treatment Plant

Pharmaceuticals were also found in wildlife animals and accumulations in food chains are observed.[13]

With respect to a human population getting older and increasing incidences of the so-called civilization diseases it is assumed that the amounts will further increase in the future.[14] Additionally, water scarcity becomes an emerging issue within the whole EU because of the climate change.[15] A sustainable water management and the protection of drinking water

[11] E. g. aus der Beek, T., Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A.: Pharmaceuticals in the environment—Global occurrences and perspectives. Environmental Toxicology and Chemistry 35(4), 823-835 (2016). doi:https://doi.org/10.1002/etc.3339; Wilkinson, J.L. et al.: Pharmaceutical pollution of the world's rivers. Proc Natl Acad Sci U S A 119(8) (2022). doi:10.1073/pnas.2113947119

[12] https://www.umweltbundesamt.de/die-uba-datenbank-arzneimittel-in-der

[13] Cerveny, Daniel et al., Neuroactive drugs and other pharmaceuticals found in blood plasma of wild European fish; 2021; Environment International 146 (2021) 106188

[14] Civity Management Consultants; Arzneimittelverbrauch im Spannungsfeld des demografischen Wandels; Berlin, 2017; https://civity.de/de/publikationen/arzneimittelverbrauch-im-spannungsfeld-des-demografischen-wandels/

[15] https://ec.europa.eu/environment/water/quantity/scarcity_en.htm

resources require effective risk mitigation measures and scientific knowledge about effects of micro-pollutants such as pharmaceuticals on human health and the environment.

One of the most concerning issues for human health is the development and spread of antimicrobial resistances (AMR), as they lower the availability of effective antibiotics for therapy of infectious diseases.[16], [17] Even low concentrations of antibiotics as found in environmental media due to anthropogenic contamination promote development and maintenance of AMR in bacterial populations.[18] As AMR genes are mobile within bacterial populations in the environment, their spread is progressing continuously. Therefore, the environment acts as a growing reservoir and carrier for AMR. The data show that better risk management is needed and environmental concerns shall be given greater consideration in the future. During production, use and disposal the contamination of the environment with antimicrobial substances has to be minimized in order to counteract the loss of effectivity of antibiotics.

Although at the time of the amendment of Directive 2001/83 in 2004 the inclusion of ERA in the authorisation of new medical products seemed to be a milestone for the minimisation of environmental impacts, it appears to be not sufficient to minimise pharmaceutical residues in the environment in the current form. The 'Guideline on the environmental risk assessment of medicinal products for human use' was adopted in 2006 (supported by the 'Question and Answer' document) and gives scientific advice how an ERA has to be conducted.[19] Since this date, environmental fate and effect data become available for new active substances, that is the major benefit of the current regulation.

The EU Strategic approach to pharmaceuticals in the environment [20] includes measures to ensure greater protection of the environment against pharmaceutical residues. It covers the whole lifecycle of pharmaceuticals from development to production, use and disposal. For some actions, best practice guidelines e. g. on the prudent use of medicines for medicinal professionals are needed. For others, legal changes in the pharmaceutical legislation or European environmental frameworks are required.

Consequently, the pharmaceutical strategy[21], published in 2020, addresses environmental challenges as one of the flagship initiatives. For implementing the aims of the pharmaceutical strategy, the EU Commission initiates the revision of the general pharmaceutical legislation. The inception impact assessment on 'Evaluation and revision of the general pharmaceutical legislation' addresses the enhancement of environmental sustainability of different aspects during production, authorisation, use and disposal of pharmaceuticals, as well as the procurement, advertising and prescribing.

Furthermore, data availability plays a central role in the chemicals' strategy and the 'one substance one assessment' approach of the European Commission. One aim of the "Chemicals Strategy for Sustainability is that "data should be easily findable, interoperable, secure, shared and reused by default". However, the chemicals' strategy and the 'one substance one assessment' approach need to be operationalized among others in the pharmaceutical legislation.

[16] https://www.umweltbundesamt.de/publikationen/antibiotics-antibiotic-resistances-in-the

[17] Larsson, D.G.J., Flach, C.-F.: Antibiotic resistance in the environment. Nature Reviews Microbiology 20(5), 257-269 (2022). doi:10.1038/s41579-021-00649-x

[18] Gullberg E, Cao S, Berg OG, Ilbäck C, Sandegren L, Hughes D, et al. (2011) Selection of Resistant Bacteria at Very Low Antibiotic Concentrations. PLoS Pathog 7(7): e1002158. https://doi.org/10.1371/journal.ppat.1002158

[19] EMA/CHMP/SWP/44609/2010 Rev. 1 & EMEA/CHMP/SWP/4447/00 corr 2*, June 2006

[20] COM (2019) 128 final;

[21] https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf

2 Strengthening the environmental risk assessment (ERA) in the authorisation of human medical products

2.1 The ERA today

For all new market applications an ERA is required in accordance with Article 8 (3) of Directive 2001/83/EC. This includes the evaluation of the risks and specific arrangements to limit impacts of the medicinal product in accordance with 1.6 of Annex I. Article (8g) stipulates "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".

The introduction of the ERA has had a positive impact on knowledge of fate and effects of active substances in the environment. Many applicants of new medicinal products recognised the need of addressing environmental risks. In most cases particularly for new active substances applicants provided the ERA according to the guideline documents. Data are now available for around 347 substances. However, according to article 1 (28a) of Directive 2001/83/EC, the environmental impact is not part of the benefit-risk assessment. Furthermore, incomplete or scientifically unacceptable ERAs do not constitute a ground for refusal. For this reason, ERA issues are automatically treated as other concern in marketing application procedures with hardly any consequences:

- For pharmaceutical products with identified environmental risks, the only consequence is the recommendation for disposal instructions. It is not legally binding. The specific arrangements to limit impacts of products on the environment are neither reflected in the relevant templates for the product literature[22], nor included in the patient information or on the packaging of the product.
- In case ERA data are incomplete at the time of a marketing authorisation, a request for providing the missing information post-authorisation is just a recommendation. In consequence, if commitments made by the applicants are in certain cases delayed or remain unfulfilled, this does not result in any direct consequences for the marketing authorization holder (MAH).
- Medicinal products can be approved without a sufficient ERA and without consequences for the product or the MAH. Especially, in decentralised marketing authorisation procedures this is common practice in order to accelerate the authorisation process.
- Referral procedures to complete the ERA or to harmonise product information between several products due to environmental concerns are not possible with respect to the current legislation.
- The scope of the ERA and main approaches are not described in detail in the legislation or its annex. The current ERA guideline is not even mentioned in the legislation as a guidance to follow. This makes it even more difficult to find agreements between applicants and assessors but also between assessors from different MS during the procedures.

[22] Directive 2001/83/EC Art. 11, 54 & 59

- The current ERA guideline exclusively addresses ecotoxicological risks and hazards, however effects to human health via the environment (e. g. drinking water protection, AMR) are not considered because protection goals are not laid down in the legislation.
- A re-evaluation of the ERA is not foreseen. Furthermore, ERA is not part of pharmacovigilance. In consequence, there is no way to include new information on environmental risks in the product literature or to re-evaluate a product in case of new scientific information.
- ERA experts are not part of the committees for human pharmaceuticals and no permanent working group or working party for environmental issues is installed e.g. at EMA. Thus, environmental issues are not sufficiently addressed within the regulatory context.

2.2 UBA proposals for ERA improvement

Environmental safety should be equally weighted in the course of marketing authorisation procedures as other non-clinical safety issues. This requires an ERA with all necessary data to derive final conclusions and an obligatory catalogue of risk mitigation measures if environmental risks or hazards are identified. For implementation in the new legislation UBA suggests the following changes to Directive 2001/83/EC[23]:

To define the lack of a complete and suitable ERA as stand-alone ground for refusal.

This should be introduced in Article 26 (1). It ensures that the ERA will be provided in a complete form including a reliable assessment of the environmental impact and effective risk mitigation measures and in a timely manner before the finalization of authorization procedures. Only in exceptional cases a post-authorisation measure for ERA completion might be considered and should be conditional which can be included in Article 22.

To include undesirable effects on or via the environment in the benefit-risk analyses

This can be done by removing 'first ident' from the text in Article 1, 28a. It ensures that the environmental impact is weighted in a proportional way in the whole process. We would like to emphasise that the overall aim of including environmental impacts in the benefit-risk assessment is not the refusal of authorisations. The resolution of the European Parliament says that "…marketing authorisations are not delayed nor refused solely on the grounds of adverse environmental impacts"[24] .It is fully acknowledged that the benefits of human medicines to patients practically always outweigh risks to the environment. However, it should be possible to decide on consequences for marketing and the use of a pharmaceutical product because of adverse environmental effects including risks to public health.

To include a description of the main targets of an ERA in the legislation

These targets may include in Annex I of the Directive:

- conclusions on the environmental risk and hazard assessment
- consideration of risks via the environment to human health e. g. contamination of raw water resources, spreading and developing of AMR
- derivation of emission limit values for manufacturing sites (see chapter 5)

[23] It is acknowledged that numbering of the articles in the new legislation may change.

[24] B9-0242/2020

The legislation should make clear that the ERA guideline has to be followed for the assessment of environmental impacts.[25]

The description of the targets is necessary to decide if the ERA lacks some necessary information which could become a stand-alone ground for refusal.

To include environmental aspects in the pharmacovigilance part of the legislation.

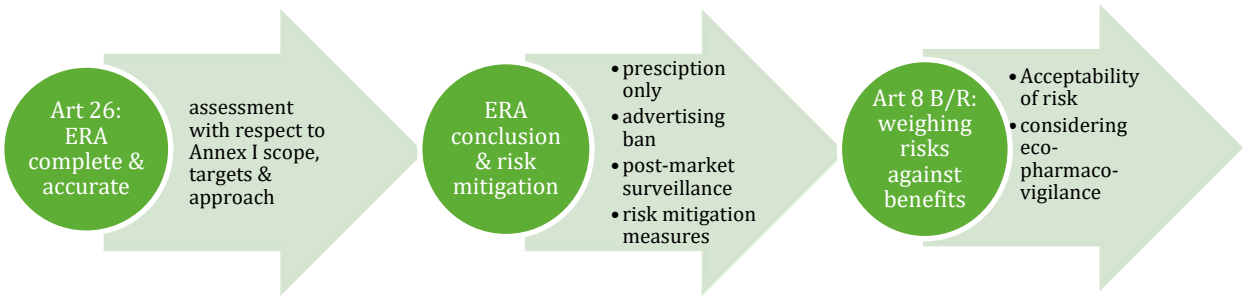
If environmental risks are part of the benefit-risk-analysis they might have been considered in the pharmacovigilance system (Title IX). Reports on the environmental impacts of active substances should become part of the pharmacovigilance report. This process makes it possible to consider risks not identified at time of authorisation.

To include risk mitigation measures in the market authorisation such as:

- Products with adverse environmental impacts should be generally considered for prescription only. Therefore, add new idents under Article 71.
- No advertising for over-the-counter medicines which pose a risk to the environment, so as not to create incentives to consume those products. This needs a new point in Article 88.
- A surveillance system for substances with adverse environmental effects and properties (see also Chapter 4) which could be included in Annex I Part 2 conditions.
- Individual product specific risk mitigation measures. Therefore, a section 'environmental properties' have to been foreseen in the SmPC (Article 11) and Article 54 and 59 have to be revised for including environmental information and risk mitigation measures.

Overall, the improvements would lead to a higher importance of ERAs in authorisation procedures. UBA expects that this will not only improve the quality of the ERA but also increase expert knowledge at Member State level and at European Medicines Agency. Clear requirements at the legal level ensure equal treatment of all applicants.

Figure 1: UBA proposal for ERA in authorisation procedures in the revised Directive



Source: own illustration, Umweltbundesamt

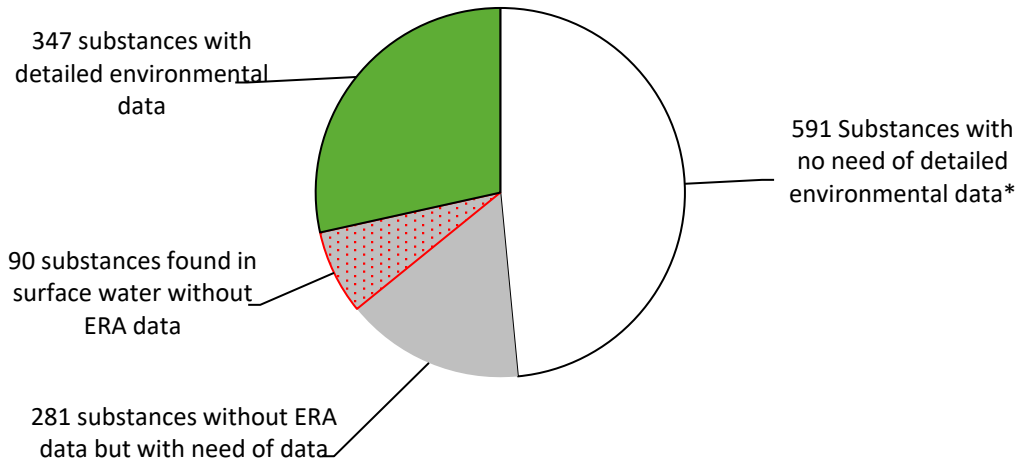
[25] Please see Regulation 2016 / 6, Annex II; IIIa3A6: Environmental Risk Assessment

3 Closing data gaps and providing transparency of environmental information

3.1 Poor environmental data availability

The review of ERA data for active substances on the German market showed that for many relevant substances no ERA data have been submitted [26]. Active substances used in large amounts are often the ones without environmental data. According to UBA's internal database, there is no ERA available for 281 active substances, 90 of them[27] have been detected in European surface waters (Figure 2).

Figure 2: Availability of ERA data for active substances on the German market (1219 substances in 2021) – relevance is given by substance characteristics



* This means predicted environmental concentration (based on the current market evaluation) in surface water is below a threshold value of 0.01 µg/l and it is no substance with a specific toxicity profile e. g. endocrine active substances
Source: own illustration, Umweltbundesamt

There are two main reasons for this lack of data:

- Legacy products approved before 2006 generally lack an ERA, but are still widely used.
- The legal requirement of providing ERAs for known active substances as generics[28] has never been fully implemented. According to the guideline[29], ERA studies can be waived if it can be demonstrated that an increase in the exposure of the environment to the active substance is not to be expected.

Hence, there are many medicinal products on the market whose environmental impact has never been investigated. Vice versa, in cases where the exemption is not met for the same active

[26] D. Gildemeister, A. Hein, U. Brandt, A. Buck, S. Hickmann & I. Rönnefahrt; Human pharmaceutical substances – identification of data gaps for environmental risk assessment (ERA); UBA_PPT (umweltbundesamt.de)

[27] The other substances were not detected or not included in any of the monitoring campaigns.

[28] Directive 2004/27/EC amending Directive 2001/83/EC Art 8 (ca) and Art. 10 (1)

[29] EMEA/CHMP/SWP/4447/00 corr 2

substance several tests in applications of different products were provided. This leads to increased costs and resources for applicants and assessors. Specifically, generic products with reference products authorised after 2006 which included a new active substance at this timepoint are affected. For vertebrate (fish) studies this does not go in line with the 3Rs principle.[30] Voluntary data sharing between applicants remains the exemption.

When data on active substances are provided within an authorisation procedure it is not ensured that these data are publicly available or easily retrievable for the public or interested parties for the following reasons:

- These data are not available in a centralised inventory of active substances but only as main results (study endpoints) in the (European) public assessment reports (EPAR or PAR) of the products. These EPARs and PARs are available on either of two different platforms: EMA or HMA (Heads of medicines agencies). In consequence, environmental information on active pharmaceutical substances are difficult to find.
- ERA data submitted following the initial market authorization are often not published due to missing updates of existing (E)PARs.

This is in contradiction to Art. 2(3)(b) Aarhus Convention assuring the public access to environmental information.[31]

3.2 UBA proposals for improving data availability

Environmental data should be available for all substances of potential environmental concern. In order to minimize the deficits, the new legislation should include the following provisions:

Catching – up procedure for those substances with missing ERA data

Assessments are needed for substances without environmental data but possible inputs to the environment. UBA acknowledges that it would take a longer time period to collect and evaluate all required data e. g. 10 – 15 years. Consequently, a priorisation scheme might be required. UBA suggests a simple system basically considering e.g. predicted environmental concentrations (PEC values) starting with substances detected in the environment or a stepwise evaluation of pharmaceuticals groups starting with most relevant ones.

Establishing of a uniform, user friendly data-base for all environmental information preferably by EMA or ECHA.

UBA supports the idea to use data platforms already used on a European level e. g. DG ENV's Common Open Platform on Chemical Safety Data (COPCSD). This could be considered as a key technical enabler of the 'one substance, one assessment' approach where authorities have access to a common dataset to fulfil their mandate under applicable legislation.

Data sharing between applicants

For vertebrate tests data sharing should be mandatory according to the 3 R Principle. For non-vertebrate tests joint data submission is highly recommended to prevent parallel submissions for products containing the same active substance.

[30] Directive 2010/63/EU: Replace, Reduce, Refine

[31] Oelkers, K., Floeter, C.: The accessibility of data on environmental risk assessment of pharmaceuticals: Is the marketing authorisation procedure in conflict with the international right of access to environmental information? Environmental Sciences Europe 31(1) (2019). doi:10.1186/s12302-019-0256-3

Establishing 'environmental monographs' on active pharmaceutical substances

The monograph system collects and summarizes all available information on active substances provided in different market authorization procedures or generated within the catching – up procedure. Reliable data from literature or project databases like the Innovative Medicine's Initiative Premier project[32] could be considered as far as possible. It is possible that the derogation of data submission in the current legislation for generic products is extended to the ERA.[33] Then no ERA would be required for products with "older" substances e. g. generics. Such facilitation would be in line with the pharmaceutical strategy intending the acceleration of procedures and minimising the efforts by the authorisation However, as most reference products do not contain any ERA data, this is extremely worrying in view of the data gaps for substances enter the environment. It also would contradict the aims of the Green Deal and the Zero Pollution Ambition and prevent an adequate risk management. Hence, UBA highly supports the idea of establishing 'environmental monographs' on active pharmaceutical substances.[34] [35] The monograph system would allow the acceleration of the authorisation procedures not on costs of environmental protection.

Such a system is independent from the application procedure and requires all marketing authorisation holders for a shared responsibility. Similar systems have been established for industrial chemicals regulated under REACH, biocides and plant protection products. Once established, the evaluated information / ERA can be used in all medicinal products for including the conclusion in the product literature and including risk mitigation measures if required. A regular re-evaluation of data and results of surveillance of substances with a risk can be implemented to ensure that all data are suitable for up to date risk assessments (see also chapter 4). The feasibility of such a monograph system for veterinary medicinal products has been evaluated recently. The authors concluded that a monograph system is justified, proportionate and affordable. [36] In UBA's point of view establishing a monograph system is the only solution to prevent a loss of environmental safety in case the derogation for ERA data submission for generic products is implemented.

[32] Prioritisation and Risk Evaluation of Medicines in the EnviRonment; https://imi-premier.eu/

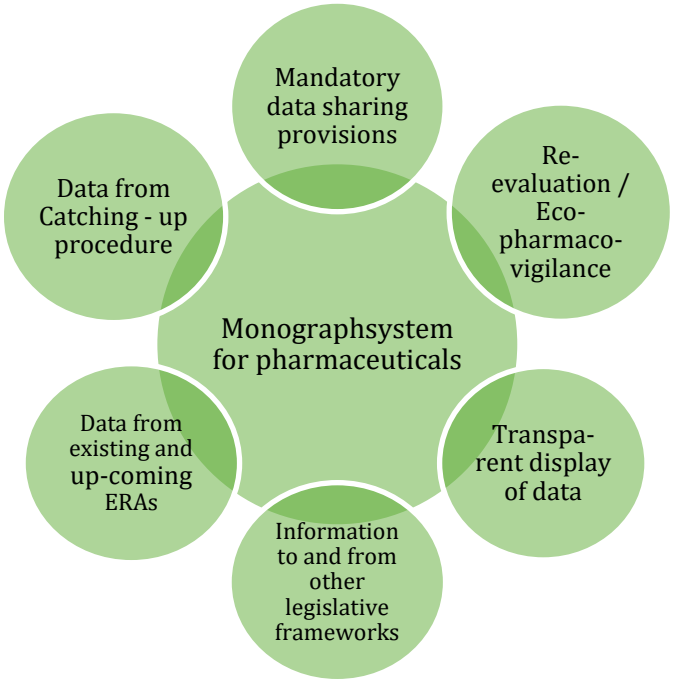
[33] Directive 2001/83/EU; Art 10 (1),(3),(4)[34] Umweltbundesamt, in prep: Monographs of Environmental data for active substances in Veterinary Pharmaceuticals,

[34] Umweltbundesamt, in prep: Monographs of Environmental data for active substances in Veterinary Pharmaceuticals,

[35] de la Casa-Resino, I., Haro Castuera, A., Casimiro Elena, R., Rubio Montejano, C., Carapeto García, R.: European legislation for veterinary medicines: Would a monograph system improve the environmental risk assessment? Integrated Environmental Assessment and Management 17(6), 1274-1285 (2021). doi:https://doi.org/10.1002/ieam.4431

[36] Floeter, C., Schwonbeck, S., Vidaurre, R., et al., 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, 2021, https://data.europa.eu/doi/10.2875/94477

Figure 3: Elements of a monograph system for environmental data for pharmaceutical active substances



Source: own illustration, Umweltbundesamt

4 Positioning of pharmaceutical legislation within other EU regulations and strategies

4.1 Missing coordination between different legislative frameworks

The current legislation on human medicinal products does not address the environmental issues in a satisfactory manner. As a matter of fact, also the coordination of actions with other regulations dealing with environmental issues remained almost completely neglected. [37, 38] For example, the data generated in the context of the marketing authorisation of medicinal products are generally not allowed to be used for the derivation of environmental quality standards (EQS-values) according to the Water Framework Directive (WFD). The same problems arise when maximum drinking water values are calculated and derived - here, too, the toxicological data are usually not available.

Vice versa, if a substance is identified to cause environmental adverse effects or detected in higher concentrations in environmental compartments because of requirements in other (environmental) frameworks this will not be considered in the ERA. This can also be attributed to the fact that environmental legislation sets quality standards for pesticides (plant protection products and biocides) in the environmental media, but not yet for pharmaceuticals (see Table 2). Under the WFD, monitoring data generated by the watch list mechanism support the inclusion of selected pharmaceuticals and antibiotics to the list of priority substances which is currently under review. There are no obligations for the MAH to take any action in preventing environmental damage when such findings were communicated. This hampers an efficient risk assessment and risk mitigation which is aimed at the zero-pollution ambition.

Table 2: Considerations of pharmaceuticals in some EU legislations considering environmental issues

EU Legislative framework	Year of adoption	Consideration of pesticides[1)]	Consideration of pharmaceuticals	Current EU action
Water Framework Directive (2000/60/EC)	2000	Annex VI, Part A Annex VIII	No	-
Directive on Environmental Quality Standards (Directive 2008/105/EC amended by 2013/39/EU)	2013	Art. 7a, Substances in annex (EQS)	Art 8b Watchlist, Art 8c strategic approach	Review of priority substances[2)], Fulfilling strategic approach pharmaceuticals[39]
Groundwater Directive (2006/118/EC)	2006	Annex I: Groundwater quality standards	No	-

[37] Freriks, A., Keessen, A., van Rijswick, M.: The Clash of the Titans; The Relation Between the European Water and Medicines Legislation. Common Market Law Review, 1429-1454 (2010).

[38] Oelkers, K.: Is the objective of the Water Framework Directive to deal with pollutant emissions at source coherently implemented by the EU's substance-specific legal acts? A comparison of the environmental risk control of pharmaceutical legislation with the REACH-, Biocidal Products- and Plant Protection Products Regulation. Sustainable Chemistry and Pharmacy 20 (2021). doi:10.1016/j.scp.2021.100386

[39] European Commission, Directorate-General for Environment, Update on progress and implementation : European Union strategic approach to pharmaceuticals in the environment, Publications Office, 2020, https://data.europa.eu/doi/10.2779/037747

EU Legislative framework	Year of adoption	Consideration of pesticides[1)]	Consideration of pharmaceuticals	Current EU action
Sewage Sludge Directive	1986	No	No	revision proposed, impact assessment closed
Urban Waste Water Directive	1991	No	No	in revision
Industry Emissions Directive	2010	Annex I: Chemical industry / production	Annex I: Chemical industry / production	draft of revision published in 2022
Classification, labelling & packaging regulation	2008	YES	No	Revision planned
Revised Drinking Water Directive	2020	(17) Recital Annex I Water quality	(7), (17) Recital Art. 13 8. Monitoring Art. 19 3. Evaluation	-
Soil Health Law	Open	Open	Open	Proposal in 2023

1) regulations on plant protection products and biocides

2) watch list (established in 2015, updates: 2018, 2020, 2022): pharmaceuticals substances included and now proposed as candidates for priority substances

4.2 Proposals for links between pharmaceutical and environmental regulations

Transparency of data for all legal requirements

A sustainable regulation across different legislative frameworks requires the possibility to use the provided data from the authorization procedure. Data received during authorisation are validated by competent authorities. Such data are best suitable for the derivation of environmental quality standards or threshold values for various environmental compartments. To facilitate monitoring and the derivation of EQS the data from the ERA of pharmaceuticals needed to be made accessible to the competent authorities in the EU. There should be no limitation by confidential restrictions, non–clinical data provided to national competent authorities (NCA) in the EU should be shared by the NCAs for all legal requirements.

Integrating pharmaceutical legislation in the Zero Pollution Ambition Cycle

The pharmaceutical legislation should become part of the Zero Pollution Ambition Cycle which is a cross regulatory approach for improving the regulatory frameworks for the systematic protection of air, water, soil and human health.[40] This means if monitoring data derived or collected from other legislative requirements are available, NCAs are responsible to include these data in the ERAs of the substances and if required set risk mitigation measures. Links to the pharmaceutical legislation in other relevant environmental frameworks and availability of the monitoring data have to be implemented by the next revisions.[41] A monograph system for

[40] Umweltbundesamt (2021) The Zero Pollution Action Plan as a chance for a cross-regulatory approach to pollution prevention and reduction | Umweltbundesamt,

[41] Same as for regulation 2019 / 6 on veterinary pharmaceuticals

active pharmaceutical substances could be used as central tool for exchange and collection of data between regulations (see chapter 3).

Identifying substances for environmental regulations

In addition, the new pharmaceutical legislation should set direct linkages from ERA results to other regulatory frameworks (Table 2) in line with the 'one substance one assessment' approach. Active substances with identified environmental risks or hazards should be set as candidates for including in the watch list under the Water Framework Directive or in future watch lists for groundwater and soil. The identification of possible candidates should be included as new ident in Annex I part 2 conditions of Directive 2001/83/ EC. Decisions about nomination have then to be followed in the other regulations e. g. WFD. For these substances re-evaluations of the ERA are needed in regular time frames.

Considering Pharmaceuticals under CLP

Possibilities to include pharmaceuticals (human and veterinary) in the classification, labelling and packaging (CLP) regulation to ensure harmonisation of environmental assessment of the active substances e. g. PBT assessment should be checked. It could be a way forward to use the same classification criteria and to communicate them in the summary of products characteristic but to refrain from labelling for human pharmaceuticals in or on the package. This will ensure a harmonised assessment without alarming the patients.

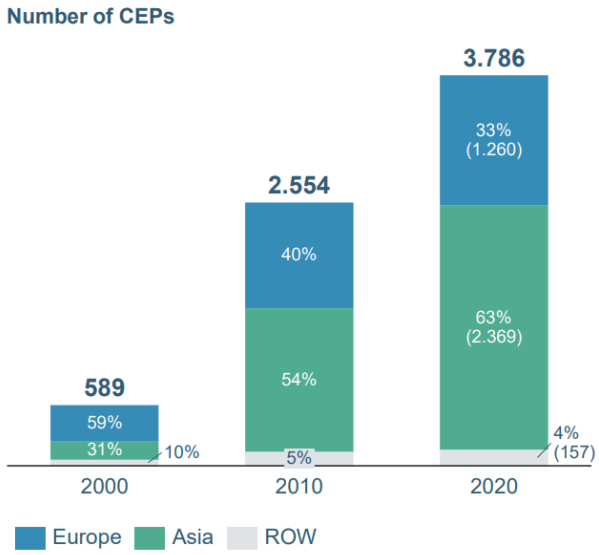
5 Making production more environmentally sustainable

5.1 Tracking the emissions from production sites

Currently, emissions of active substances from pharmaceutical manufacturing sites into the environment are not considered in the pharmaceutical legislation. Generally, the potential risks of such emissions are difficult to assess due to a lack of transparency on manufacturing sites and the fact that active pharmaceutical substances are mainly manufactured in countries outside European Union. In 2020, more than 60% of the CEPs[42] are hold in Asia (Figure 4).

At some production sites it has been demonstrated that emissions from industry pose a direct threat for the health of the local population. The spread of antimicrobial resistance from such hotspots is a global challenge.[43]

Figure 4: Development of the number of valid CEPs[37] 2000 – 2020



ROW = Rest of World

Source: "Where do our active pharmaceuticals come from? A world map of API Production", Mundicare life Science Strategies, Berlin, September 2020

According to Directive 2001/83/ EC manufacturers are obliged to comply with the principles and guidelines of good manufacturing practice (GMP). [44, 45] In consequence, quality standards of the medicinal products and the starting materials of active substances apply also to producers outside the EU. The WHO has already emphasized the importance of environmental issues with respect to antimicrobial resistances within the current WHO GMP[46] . Elements of the GMP like control of raw materials, processes and waste management offer a good possibility to raise

[42] Certificate of Suitability of Monographs of the European Pharmacopoeia, proof of active pharmaceutical ingredients quality, used for drug approvals

[43] Larsson, D.G.J., Flach, C.-F.: Antibiotic resistance in the environment. Nature Reviews Microbiology 20(5), 257-269 (2022). doi:10.1038/s41579-021-00649-x

[44] 2001/83/EC Article 47; Regulation No. 1252/2014

[45] Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC as regards the principles and guidelines of good manufacturing practice (GMP) for medicinal products for human use.

[46] WHO Technical Report Series, 986Annex 2, 2014

awareness for environmental issues among manufacturers and GMP inspectors. However, this approach is not legally binding and does not solve the problem in its entirety.

In the EU there is no union-wide environmental regulation for pharmaceutical manufacturing. Active pharmaceutical substances are not regulated under REACH and hence restrictions are not set under this framework. Furthermore, the pharmaceutical industry falls under the scope of the Industrial Emissions Directive[47]. Here, it has been covered by the BREF for the manufacture of organic fine chemicals (OFC)[48]. However, the OFC BREF will not be reviewed and updated.[49] Therefore, emissions from the pharmaceutical industry are only generally covered in the CWW (Common Waste Water) and WGC (Waste Gas Treatment/Management Systems in the Chemical Sector) BREFs. Issues to be considered for the pharmaceutical industry in particular emission limit values for active substances are not considered. These two BREFs neither address or stipulate emission levels associated with best available techniques, nor elaborate requirements for production-integrated measures for the production of pharmaceutical products and its intermediates. The CWW and WGC BREFs both focus on end-of-pipe techniques and achieved emission levels for the chemical industry in general.

Furthermore, the proposal for a Directive on Corporate Sustainability Due Diligence (CSDD)[50] does not consider pharmaceuticals.

5.2 Proposals for limiting the industrial emissions of pharmaceuticals

A global solution is needed for considering the environmental impact of the manufacturing of pharmaceuticals. Transparency on the supply chain should be mandatory for products marketed in EU and environmental impacts along the supply chain should be tracked.

The new legislation should ensure high environmental standards during manufacturing of active substances and medicinal products intended for the EU-market. This requirement has to be met regardless of whether the production site is located inside or outside the EU.

Establishing emission limit values

UBA proposes to enable the European Commission to establish Emission Limit Values (ELVs) for active substances, means including a new legal act on emissions / discharge. If necessary the ELVs can be implemented by prioritizing the substances /substance groups according to their highest concern e. g. beginning with antimicrobial substances to prevent the distribution of antimicrobial resistances in the environment. For the derivation of an ELV, data provided within the ERA and any available additional information should be used.

Including environmental standards under GMP

In this context, the scope of GMP should be extended to include environmental emissions and that requirements relating to ELVs became part of the definition of GMP. Including environmental standards under GMP would have the following advantages:

- New legal requirements can be implemented in an established framework for regulatory control and action
- Control of the whole production chain would be possible.

[47] IED 2010/75/EU

[48] Best available techniques reference document: OFC BREF August 2006

[49] Decision of the Commission (DG ENV C4), IED Art. 13 Forum in December 2017

[50] COM (2022) 71 final

- Same rules would apply to manufacturers in the EU and in third countries.

European competent authorities should develop guidance for the suitable monitoring of emissions. Here technical details should be included for the measurements to ensure compliance with the limit values. It is acknowledged that the main task of GMP is to assure a high quality of medicinal products. Including environmental issues would be a new task and means higher efforts. This means specific training of inspectors and an increasing work load. However, in order to achieve a higher level of environmental safety in production, control of compliance with standards by an independent inspector and not by the industry itself is indispensable. The corresponding resources should be made available. This can save human lives.

Introducing a declaration of compliance

An additional declaration of compliance as part of the authorization procedure could facilitate the work for all stakeholders. Such a declaration can be used as a documentation at GMP inspections and should be updated in regular timeframes.

Considering pharmaceuticals in CSDD and BREF

In addition, considering pharmaceuticals under the Directive on CSDD could help to identify and mitigate risks in the value chain.

At the European level the existing but outdated 2006 OFC BREF should be reviewed and updated. The decision taken by the European Commission in 2017 to refrain from a revision should be reconsidered and specific arrangements for pharmaceutical active substances should be included so that the competent authorities can implement this relevant concern in the permits they grant.

6 Key areas of action

We appreciate that the revision of the general pharmaceutical legislation will contribute to a better identification and mitigation of environmental risks of human medical products and to achieving the goals of the zero-pollution ambition. The current legal situation is not sufficient to minimise pharmaceutical residues and risks to the environment and to human health. A combination of various measures along the whole life cycle of medicinal products is necessary to reduce the environmental footprint of pharmaceuticals significantly and allows efficient risk mitigation and management. In particular, we identified five key areas of action within the current revision process:

1. Ensure data completeness and enforce risk mitigation by making the ERA and its consequences a ground for refusal and including it in the benefit-risk balance.
2. Close the data gap by implementing a framework for a catching-up procedure.
3. Increase data availability and transparency by means of substance monograph system. Make data easily retrievable in an EU database.
4. Build a comprehensive risk management system. Create a living, transparent system of data exchange between the pharmaceutical legislation and legislations considering environmental issues.
5. Protect the environment globally from adverse effects of pharmaceutical residues particularly from manufacturing by providing a level-playing field for manufacturers inside and outside the EU and applying legal standards for environmental protection to manufacturing of active substances and pharmaceutical products for the European market.

We are convinced that in this way the protection of the environment can be strengthened without compromising availability of medicines. A high level of environmental safety ensures a high level of health protection.

List of Abbreviations

AMR	Anti-microbial Resistance
BREF	Best available techniques Reference Document
CEP	Certificate of suitability of Monographs of the European Pharmacopeia
CSDD	Corporate Sustainability Due Diligence
CWW	Common Waste Water
DG ENV	Directorate-General Environment
ELV	Emission Limit Values
EMA	European Medicine Agency
(E)PAR	(European) Public Assessment Report
EQS	Environmental Quality Standard
ERA	Environmental Risk Assessment
EU	European Union
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agency
MAH	Market Authorisation Holder
MS	Member State
NCA	National Competent Authority
OFC	Organic Fine Chemicals
PEC	Predicted Environmental Concentration
3 R	Re-place, Reduce, Refine
ROW	Rest of World
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
UBA	German Environment Agency (Umweltbundesamt)
WFD	Water Framework Directive
WHO	World Health Organisation
WGC	Waste Gas Treatment/Management Systems in the Chemical Sector