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POLICY OPTIONS FOR REGULATING PHARMACEUTICALS IN THE ENVIRONMENT

Releases of pharmaceuticals into the environment: an issue of growing concern

Over 100,000 tonnes of pharmaceutical products are consumed globally every year (24% in Europe). During their manufacture, use and disposal, Active Pharmaceutical Ingredients (APIs) as well as other chemical ingredients are released into the environment (BIO Intelligence Service, 2013).

A very substantial share of pharmaceutical production now takes place overseas. This is particularly the case for antibiotics and other generic medicines. China produces 80-90% of antibiotic APIs and Indian companies lead the production of finished dose products. There have been numerous high-profile pollution scandals at antibiotics production sites in both China and India, resulting in the spread of drug-resistant bacteria (Changing Markets, 2016). Possible downstream pollution from manufacturing plants has been observed in the EU and other parts of the world (BIO Intelligence Service, 2013).

APIs are released in high amounts to the environment during human and veterinary consumption of drugs, as between 30 and 90% of an oral dose is excreted in urine as an active substance. A global review shows that over 600 different APIs have been detected in the environment (Lyons, 2014), in some cases at levels that pose a high risk to the environment. Pharmaceuticals have also been monitored in drinking water, waste-water, sewage sludge and soils (BIO Intelligence Service, 2013).

3000 APIs are marketed in the EU as human or veterinary drugs. Although the environmental impact of most of these substances is widely unknown, several API are known to persist and to accumulate in the environment. Examples of ecotoxicological effects of APIs include the contraceptive ethinylestradiol, which impairs the reproduction of exposed fish populations; the effects of various antibiotics on environmental bacteria and algae or the decline of vulture populations due to poisoning with diclofenac when feeding on animals carcases (BIO Intelligence Service, 2013).

The most relevant pharmaceuticals for the environment are anticancer medicinal products; hormonally active substances and antibiotics. Hormonally active APIs such as EE2 (which is present in the birth control pill) or paracetamol (over-the-counter pain reliever and a fever reducer) can disrupt the normal functioning of the endocrine system.

The presence of antibiotics in the environment contributes to the development of antimicrobial resistance (AMR), one of the major emerging threats to human health today. AMR burden in terms of lives lost, morbidity, and healthcare expenses and productivity losses is much greater than currently available statistics suggest - 25,000 deaths in 2007 - (ECDC, 2009) and projections estimate a 15 fold increase in

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morbidity in Europe due to AMR by 2050 with 390,000 deaths (Deloitte Sustainability, 2017). While many questions remain unanswered regarding the transmission dynamics between antibacterial agents in the environment and the development and spreading of drug resistance in people, it is clear that the rise of so-called superbugs could throw us back into a "pre-antibiotic era", with all the serious consequences this would entail for healthcare systems and people. From treating complex diseases including cancer, diabetes, pneumonia or HIV/AIDS, to performing surgeries to childbirth, AMR could put an end to many key achievements in health of the last century given the crucial role played by antibiotics (EPHA, 2017).

PHARMACEUTICALS, AN UNREGULATED INDUSTRY

Despite the high concerns on the threats posed by pharmaceuticals, their releases into the environment are almost unregulated:

- Information on environmental impacts of APIs is not available to the public or authorities. Accessibility is generally limited to risk assessors only.
- The assessment of the environmental risks is only compulsory for the Human Medicinal Products (HMP) placed on the market after October 2005, therefore, it covers only a minority of pharmaceuticals. Submitted Environmental Risk Assessments (ERA) may be incomplete or altogether absent from the marketing application (in Germany, for the top 10 human medicinal products found in surface water not a single ERA was available).
- ERAs' results are not considered for the decision on granting market authorisations of HMP, and the proposed risk mitigation measures are not binding.
- There are insufficient monitoring requirements and no specific emission limits in place for API releases from manufacturing plants in or outside Europe.
- Good Manufacturing Practices do not take into account the risks that medicinal products may pose to the environment and human health at the manufacturing stage.
- There are no limits in place for the content of pharmaceuticals in drinking water, in surface water, or waste water, not even from hospitals' effluents.
- Although pharmaceuticals contain hazardous substances, there are no specific regulations for the management of most human and veterinary medicinal products waste (only cytotoxic and cytostatic substances are regulated).
- There is no obligation to monitor or regulate medicinal pharmaceuticals present in sewage sludge or in manure used in agriculture.

REGULATORY NEEDS

As well as other chemical pollutants such as pesticides, biocides or industrial chemicals, the emission of pharmaceuticals into the environment needs to be regulated:

- **To ensure adequate information and transparency on the environmental impacts of pharmaceuticals.**
- **To ensure adequate and reliable evaluation of environmental risks of pharmaceuticals.**

- **To prevent environmental releases of pharmaceuticals throughout their life-cycle.**
- **To control emissions of pharmaceuticals to the environment when prevention is not feasible.**

A. To ensure adequate information and transparency on environmental impacts.

Information on the ecotoxicological properties is lacking for most of the pharmaceuticals on the market. Existing information is provided in the ERA performed by industry and is scarce, scattered in individual reports, heterogeneous, incomplete and not publicly available. Toxicological effects occurring at low doses such as alteration in natural behaviours (activity, feeding rates, sociability), are normally not taken into account. Relevant studies from peer-reviewed literature are generally not included in the ERA performed by the pharmaceutical companies. Information on the presence of medicines in different environmental compartments is also scarce and heterogeneous as there is no obligation to monitor APIs in the environment, not even in water. Environmental impacts are only included in the reporting of adverse events of the veterinary pharmacovigilance system and, in any case, are reported relatively infrequently through the established tools.

Policy options:

✓ **Include medicinal and veterinary products under all of REACH titles.**

Medicinal and veterinary ingredients are exempted from most titles of REACH Regulation, including registration, evaluation and authorisation. The amendment of REACH to include pharmaceutical ingredients under all of its titles would ensure the generation of information on its ecotoxicological properties through the registration process and would improve the environmental risk assessment of APIs at all life cycle stages of pharmaceutical products. In order to avoid the bad quality and noncompliance problems of industrial chemical registrations, the registration files for APIs should be prepared by independent labs, nominated by ECHA although paid by industry. The costs could be shared by all the companies marketing the same APIs. As with industrial chemicals, deadlines could be established to ensure that all APIs in the market are registered in the near future. Priority should be given to those APIs with higher environmental relevance and used in higher volumes in the EU.

✓ **Public centralised EU electronic register of environmental impacts of API (human and veterinary).**

An alternative to the amendment of REACH, would be to create a specific register on the environmental impacts of all APIs marketed in the EU, based on the experience from REACH and also from the pesticides and biocides registration systems. In order to avoid the bad quality and non-compliance problems of existing systems, the registers of APIs should be prepared by an

independent lab as suggested above. This register would be public and accessible online in the same way as the REACH, pesticides and biocides registers.

✓ **Effective ecopharmacovigilance system both for human and veterinary pharmaceuticals.**

The EU legislation for HMP (Directive 2001/83/EC) should be amended in order to introduce environmental impacts reporting requirements in the human pharmacovigilance system. The importance of reporting environmental impacts, in particular AMR, should be promoted among professionals and authorities and the reporting tools should be simplified.

✓ **Inclusion of most relevant API in priority substance list and setting Environmental Quality Standards for these pollutants.**

In 2007 the German Advisory Council on the Environment (SRU) recommended examining the possibility of including pharmaceuticals in the list of priority hazardous substances. Environmental Quality Standards (EQS) are set for these substances in surface waters (river, lake, transitional and coastal). However, in 2018 there are still no pharmaceuticals included as priority substances despite the fact that this was already proposed by the Expert Group on Review (SG-R) of the Priority Substances in 2009.

Six pharmaceuticals have already been included in the Watch List [1] for surface waters including the painkiller diclofenac, two synthetic hormones 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) and three antibiotics (erythromycin, clarythromycin, azythromycin). No pharmaceutical is included in the Watch List for groundwater. Monitoring results show high risk levels for several of these API[2]. These APIs should immediately be included in the list of priority hazardous substances and Maximum Allowable Concentration (MAC) limits shall be set to the maximum technical feasible "detection limit". Additional relevant pharmaceuticals should be included both in the surface and in the groundwater watch lists. Improved monitoring results and target objectives to achieve a good chemical status will enable the identification of the sources and most cost-effective measures that could be taken upstream to prevent pollution.

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[1] The Watch list is a mechanism to provide high-quality monitoring information on the concentrations of potentially polluting substances in the aquatic environment to support future prioritisation exercises. The mechanism is aimed at emerging pollutants and other substances for which the available monitoring data are either insufficient or of insufficient quality for the purpose of identifying the risk posed across the EU.

[2] See EEB Briefing The environmental and health impacts caused by emissions of APIs to the environment.

- ✓ **Establish and enforce greater transparency across pharmaceutical supply chains** by obliging companies to disclose in full the origin of their products at each step of the chain and down to the company name and factory where they were manufactured.

B. Ensure adequate, reliable and transparent evaluation of environmental risks of APIs.

"A reliable and relevant prospective risk assessment procedure is the backbone of an effective and successful environmental policy." (Ågerstrand, 2015)

The European Medicines Agency (EMA) guidelines for human and veterinary pharmaceuticals describe how the ERAs for human and veterinary pharmaceuticals should be performed. Important deficiencies of these guidelines that need to be tackled have been identified. The following recommendations from Ågerstrand (2015) should be implemented:

"1. Require environmental risk assessment also for products put on the market before 2006

We recommend that environmental risk assessments are performed also on products approved before the European Medicines Agency's guideline came into force. This would provide relevant environmental information for all active pharmaceutical ingredients that could be found in the environment.

2. Add requirements to assess the risk for development of antibiotic resistance

We recommend that information that enables assessment of the risk for increased antibiotic resistance development is included in the environmental risk assessment for antibiotic substances. This would provide a more accurate picture of the risks connected to the environmental occurrence of antibiotics and their risk to human health.

3. Perform only one environmental risk assessment per active pharmaceutical ingredient

We recommend that pharmaceutical companies that produce/import the same active pharmaceutical ingredient submit a joint environmental risk assessment instead of each company producing a separate one for the same substance, in line with the REACH Regulation's 'one substance, one registration' principle. This would increase consistency, and reduce animal testing as well as duplication of work.

4. Refine the tiered approach

We recommend that the tiered approach is refined to include pharmacological and toxicological data from the drug discovery process, as well as bioconcentration data. This would improve the

prioritisation process so that the ecotoxicity testing is focused on the most problematic substances and the most relevant test species.

5. Perform mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action

In order to overcome the cocktail effect problem, we recommend that environmental risk assessments are performed for groups of active pharmaceutical ingredients with similar modes of action. This would enable a more accurate environmental risk assessment.

6. Mandate use of all available ecotoxicity studies

We recommend that all available ecotoxicity studies (including independent studies), of sufficient reliability and relevance, are used in the decision process. This would make better use of the available knowledge and may therefore add important information to the environmental risk assessment.

7. Include environmental risks in the risk-benefit analysis

We recommend that environmental risks are included in the risk-benefit analysis when a product is considered for market authorisation. This would increase the importance

of the environmental risk assessment and motivate pharmaceutical companies to perform the assessment on time.

8. Require review of the environmental risk assessments at regular intervals

We recommend that environmental risk assessments must be updated when significant new environmental information is available. This would bring forward the regulatory use of new scientific data and increase collaboration between stakeholders.

9. Include data from production of active pharmaceutical ingredients and formulations in the environmental risk assessments.

We recommend that the risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in environmental risk assessments when reviewing updated dossiers of products already on the market. This would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.

10. Increase transparency

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We recommend that environmental risk assessments and information about manufacturing sites are made publicly available. This would enable use of that information for other purposes such as research and evaluation, as well as stimulate companies to take more environmental responsibility throughout their supply chains."

C. Prevent environmental releases of APIs.

Regulatory measures to prevent releases of pharmaceuticals into the environment should be implemented similarly to measures included in REACH, biocides or pesticides legislative frameworks.

✓ **Restriction of APIs already known to pose a risk to the environment.**

As pharmaceuticals are covered by REACH Restriction title, APIs that are showing already a risk to the environment in the European Union should be restricted. The Commission should ask ECHA to prepare an Annex XV restriction dossier for these APIs. Member States where high environmental levels of APIs have been monitored could also take the lead in proposing restrictions. The scope of the restriction could include, for example, marketing limitations when safer alternatives are available; risk management measures to prevent environmental releases; or limitation of use in hospitals/health care centres that have effective of waste water treatment facilities on site.

✓ **Public procurement to favour HMPs and VMPs with low environmental impacts**

Following the example of Sweden, Members States should adopt environmental procurement criteria for pharmaceuticals and their packaging including emissions from manufacturing, content of environmentally hazardous substances, and working conditions in the production phase. Under the Swedish system, suppliers must provide the required environmental information through a freely accessible Web site, such as www.fass.se. Before being published, the information is reviewed and authorised by an independent third-party expert. (Medicinal Products Agency, 2016)

D. Reduce emissions to the environment.

Emissions of APIs to the environment should be controlled throughout the life cycle of medicines, from manufacturing (inside and outside of Europe), to consumption and waste disposal. Pharmaceutical ingredients as well as their metabolites and transformation products should be included horizontally as pollutants to be controlled in all relevant environmental legislation.

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During manufacturing of pharmaceutical products:

- ✓ **Revise the Good Manufacturing Practice (GMP) legislation to include requirements for environmental protection.**

  In order to be granted a marketing authorisation, pharmaceutical products manufacturers have to comply with GMP requirements to ensure that these products are always produced and monitored in such a manner that they satisfy quality requirements that are appropriate for their intended use. A well developed and functioning inspection system is already in place for monitoring compliance with GMP. Including environmental requirements under the GMP legislation will also have an impact on manufacturers in third countries.

- ✓ **Updating the Environmental Quality Standards Directive (EQS-D) to provide MAC values for active pharmaceutical substances.**

- ✓ **Revise relevant Best Available Techniques (BAT) reference documents (BREFs) to take into account environmental emissions of pharmaceutical ingredients during the manufacturing of pharmaceutical products.**

  The Commission shall ensure that Member States fully implement the BREF related to the Common Waste Water and Waste Gas Treatment/ Management Systems in the Chemical Sector (CWW). Member States shall review operating permits of pharmaceutical sites, implement the whole effluent assessment approach, oblige mandatory monitoring of API likely to be found in waste water (following the inventory of waste water set in BAT 2) and prevent emissions of relevant pharmaceutical ingredients in waste water through the application of more effective waste water treatment techniques. Information obtained through the application of BAT2 identifying the presence of API shall be shared with other stakeholders, in particular decision-makers, authorities and NGOs working on water protection. Possible regulatory gaps identified should be addressed through strengthened upstream control instruments (e.g. IED dedicated chapter on pharmaceuticals, REACH Regulation) and be based on recent developments in green chemistry or other findings. A more systematic link of achieving the Water Framework Directive objectives with BREF requirements shall be made. The upcoming HAZBREF initiative should address the issue of pharmaceuticals in water, considering the aforementioned elements.

During consumption

- ✓ **Obligatory prescription of APIs of high relevance for the environment.**

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EU legislation (Directive 2001/82/EC) requires prescriptions for veterinary pharmaceuticals (VMPs) which pose a potential risk to the environment, however, such an obligation does not exist for human medicinal products. The EU legislation for HMPs should be amended to require from EU MS prescription-only delivery for HMPs posing environmental risk. Guidelines should be developed both for HMPs and VMPs, for identifying environmental risk thresholds triggering prescription-only administration of APIs of high relevance for the environment.

During waste management

The large majority of unused pharmaceuticals is disposed of with municipal waste or directly in sewage. The only pharmaceutical products that are explicitly classified as hazardous waste under the Waste Framework Directive are cytotoxic and cytostatic products.

✓ **Enforce and improve provisions regarding take-back schemes in EU legislation.**

Competent authorities should ensure the enforcement of the provisions regarding take-back schemes in EU legislation on pharmaceutical products. This legislation should be amended to include specific requirements regarding Extended Producer Responsibility (EPR) and to develop an EPR system for unused medicines at the EU level, taking into account existing initiatives at MS level.

National EPR schemes should also be compliant with new minimum requirements as stipulated in revised Waste Framework Directive, to ensure the financing of the infrastructure to separate collection and proper treatment of medical waste. These EPR schemes should also be operating to reflect the waste treatment hierarchy, starting with prevention. For example, those producers offering exact amount of drugs needed rather than packaged drugs could be rewarded through fees modulation (as they will both prevent buying more drugs than needed, as well as reducing the overall amount of packaging).

✓ **Revise the Classification, Labelling and Packaging (CLP) Regulation to remove the blanket exclusion of human and veterinary medicinal products.**

This would allow the classification of relevant pharmaceuticals (in products) as hazardous (the most relevant classification would be "hazardous to the aquatic environment") and would ensure that their waste would be considered as hazardous waste and properly disposed of.

✓ **Revise the Waste Framework Directive**

To include a provision on pharmaceuticals in Annex III regarding the properties of waste which render them hazardous and to include a general provision that establishes that pharmaceutical

substances added to the priority (hazardous) substances list would automatically classify as hazardous waste.

✓ **Remind national competent authorities of the need to classify pharmaceutical wastes as hazardous waste, when appropriate**, under entry 07 05 13* (solid wastes containing dangerous substances). The Waste Framework Directive allows EU Member States to consider waste as hazardous even if it does not appear in the EU list of hazardous waste, provided it displays relevant properties.

Water

✓ **Update the Environmental Quality Standards Directive (EQS-D)** to provide MAC values for active pharmaceutical substances.

✓ **Use any future revision of** the Urban Waste Water Treatment Directive (UWWTP-D) to ensure that API are effectively treated and destroyed before further release.

✓ **Develop EU guidance for hospital/healthcare-centres to reduce contamination of municipal waste water with residues resulting from the use and disposal of pharmaceuticals.**

✓ **Amend the Groundwater Directive (GWD)** to ensure that ERA results for pharmaceutical substances are taken into account by the Commission when reviewing Annexes I and II (groundwater quality standards + list of pollutants and threshold values).

Sludge/ Manure

✓ **Amend the Sewage Sludge Directive** to require monitoring and establish protective limit values for relevant pharmaceutical substances and AMR microorganisms in sewage sludge.

✓ **Any future Commission proposal for a Soil Framework Directive** should require monitoring and establish protective limit values for relevant pharmaceutical substances and AMR microorganisms in soil.

✓ **Use ongoing revision of the Fertilisers Regulation** to ensure that manure, sewage sludge and water used as fertilisers or for irrigation are safe, by setting concentration limits for certain pharmaceuticals and AMR microorganisms in these materials, and by promoting good practices to reduce the risks of transfer to soils.

✓ **Close gaps in the BREF document on the intensive rearing of poultry and pigs** to require monitoring and establish protective limit values for relevant pharmaceutical substances and AMR microorganisms in manure and effluents. The BAT Conclusions provide a catalogue of techniques to reduce emissions of microbial pathogens to air and water from processing of manure and landspreading on farm, but do not address the use of pharmaceuticals / AMR specifically from these activities. There is just a general requirement to treat contaminated waste water, but without

specific requirement on pharmaceuticals, despite the recognition that these may end up in the manure. Building on findings gathered through the HAZBREF review, the IRPP BREF should be amended to close gaps, where necessary.

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