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Background document for public consultation on
pharmaceuticals in the environment

In partnership with Milieu Ltd, Ineris and Pr. Klaus Kümmerer
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List of Acronyms

ACS	American Chemical Society
ADEME	The French Environment and Energy Management Agency
AESGP	Association of the European Self-Medication Industry
AHEG	Ad-Hoc Expert Group
AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
BAT	Best Available Techniques
BREF	BAT Reference Document
CDC	Centres for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CIS	Common Implementation Strategy
CLP	Classification, Labelling & Packaging
CVMP	Committee for Medicinal Products for Veterinary Use
CWW	Common Waste Water and Waste Gas
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHFG	European Health Forum Gastein
EIP	European Innovation Partnership on Water
EMA	European Medicines Agency
EMAS	Eco-Management and Audit Scheme
EPAR	European Public Assessment Report
EQS	Environmental Quality Standard
EQSD	Environmental Quality Standards Directive
ERA	Environmental Risk Assessment
ERAWP	Environmental Risk Assessment Working Party
EU	European Union
FASS	Federation of Community Health Associations
FRAME	Framework to Assess and Manage Contaminants of Emerging Concern in Indirect Potable Reuse
GAP	Good Agricultural Practices
GMP	Good Manufacturing Practices
HCWH Europe	Health Care Without Harm
HHRA	Human Health Risk Assessment

HMP	Medicinal Products for Human Use
IED	Industrial Emissions Directive
IMI	Innovative Medicines Initiative
INERIS	National Institute for Environmental Technology and Hazards
iPIE	Intelligence-Led Assessment of Pharmaceuticals in the Environment
IWA	International Water Association
JRC	Joint Research Centre
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MEC	Measured Environmental Concentration
MRB	Multi-Resistant Bacteria
MS	Member State
OECD	Organisation for Economic Co-Operation and Development (OECD)
OFC	Organic Fine Chemicals
OTC	Over The Counter
PAR	Public Assessment Report
PBT	Persistent, Bio-accumulative and Toxic substance
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
PSCI	Pharmaceutical Supply Chain Initiative
PSUR	Periodic Safety Update Report
RBMP	River Basin Management Plan
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	Risk Mitigation Measure
STAMP	Safe and Timely Access to Medicine for Patients
STARE	Stopping Antibiotic Resistance Evolution
SWP	Safety Working Party
TGD	Technical Guidance Document
UBA	German Federal Environmental Agency
UWWTD	Urban Waste Water Treatment Directive
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary Medicinal Product
vPvB	Very Persistent, Very Bio-accumulative
WFD	Water Framework Directive
WG	Working Group
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant

Background document for public consultation on pharmaceuticals in the environment

Introduction

Health care and animal breeding as practised in the EU heavily rely on the administration of pharmaceuticals, which is reflected in the continuous growth of the European market for medicines for human and veterinary use¹.

Access to pharmaceuticals is essential to public and animal health and must remain a priority. However, the consumption of pharmaceuticals is also tied to their continuous release into the environment, either in the form of their original active pharmaceutical ingredients (APIs) or as metabolites or other degradation products. Although many are released in amounts considered as negligible from an environmental risk perspective, there is increasing evidence from specific exposure scenarios that some pharmaceuticals pose environmental risks (e.g. certain anti-parasitics, antimicrobials, pharmaceuticals with endocrine-disrupting effects and X-ray contrast media). Research has demonstrated the potential for endocrine-disrupting pharmaceuticals to impair reproduction in fish, and for certain antibiotics to inhibit the growth of algae. Furthermore, some pharmaceuticals could also potentially lead to adverse health effects if humans are exposed via the environment. Although several studies report very low risks for human health at concentrations generally observed in the environment or in drinking water, long-term effects on human health of chronic exposure to pharmaceuticals cannot be ruled out with current knowledge².

Practices throughout the life-cycle of pharmaceuticals, from manufacturing to disposal, contribute to their emissions into the environment and reflect a number of gaps and inefficiencies in the way pharmaceuticals are currently managed. At EU level, the issue of pharmaceuticals in the environment is mostly addressed in the legislation relating to veterinary medicinal products and to a lesser extent to medicinal products for human use. It is also addressed to some extent in the chemicals, industrial emissions, water, waste and food legislation, although most of it does not include specific provisions for pharmaceuticals. Practices are further influenced by many other factors (national legislation, economic, technical, organisational, scientific, and cultural factors), which could be acted upon to leverage more sustainable and prudent management and use of pharmaceuticals.

The present consultation is part of the effort to develop the EU strategic approach to pharmaceuticals in the environment mentioned in Directive 2013/39/EU³, which is likely to take the form of a Commission Communication⁴. The approach will be important among other things to help the EU achieve the UN Sustainable Development Goals, in particular Goal 6 ("Clean Water and Sanitation"), as well as objectives in EU legislation such as the "good status" objective in the Water Framework Directive.

¹ Human pharmaceuticals are also called human medicinal products (or HMPs); Veterinary pharmaceuticals are also called veterinary medicinal products (or VMPs).

² For an overview of environmental risks posed by medicinal products in the environment, please refer to:

- BIO IS, 2013. Study on the environmental risks of medicinal products. https://ec.europa.eu/health/sites/health/files/files/environment/study_environment.pdf
- Deloitte, 2016. Options for a strategic approach to pharmaceuticals in the environment – Scientific and technical state-of-the art.

³ Article 8b of Directive 2013/39/EU of The European Parliament and of The Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy

⁴ Roadmap: https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-2210630_en

Some issues discussed here and asked about in the consultation document are:

- Obtaining better knowledge of the issue (e.g. through fostering research and monitoring and reporting activities);
- Identifying more sustainable production, consumption and disposal patterns in line with the circular economy.

Any actions to address the risks must also ensure that the clear and undisputable benefits of the sustainable use of pharmaceuticals for human and animal life and the competitiveness of EU healthcare systems are maintained.

Based on a review of the recent literature and preliminary consultation of stakeholders⁵, 10 main potential action areas were identified and 30 possible policy options were selected for further consideration. These options are outlined below and described in detail in the section [Factsheets](#). Precise details regarding how specific options could be implemented would need to be elaborated at a later stage. The public consultation aims to collect feedback and further information from all categories of stakeholders on the actions that could be taken, in order to support the Commission in the preparation of the EU strategic approach to pharmaceuticals in the environment.

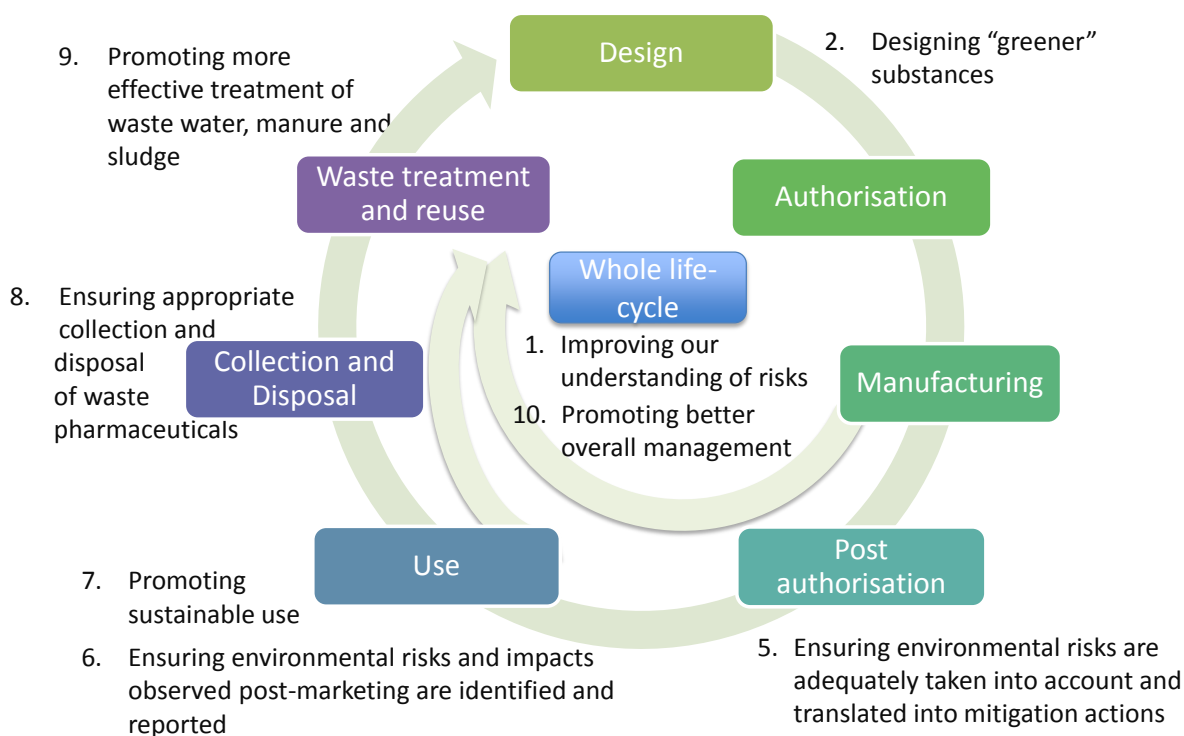


Figure 1: Ten main action areas across the life cycle of pharmaceuticals

⁵ Through a workshop organised in 2014 by the Commission and a preliminary consultation of experts from environmental and medicines agencies, academics, industry associations, NGOs in the context of the present study.

Whole life-cycle: Knowledge base

Improved understanding of the risks from pharmaceuticals to the environment

Despite the amount of new scientific evidence, information regarding environmental risks is frequently incomplete (limited data on their environmental occurrence or on their ecotoxicology), sometimes inconclusive and difficult to access at EU level for several pharmaceuticals currently on the EU market.

The scientific community still faces key challenges, such as how to determine risks associated with chronic exposure to pharmaceuticals at low doses, risks associated with metabolites and transformation products, as well as risks associated with pharmaceutical (and other chemical) mixtures in environmentally realistic settings. Further research is also needed to understand the relationship between the release of antimicrobials into the environment, the emergence and spread of antimicrobial resistance via the environment and its consequences for human and animal health. In Europe, the ECDC estimates that antimicrobial resistance (AMR) in general results annually in 25,000 deaths and related costs⁶, causing healthcare expenses and productivity losses of over €1.5 billion annually. O'Neill et al. projected a 15-fold increase in morbidity by 2050 in Europe, with 390,000 deaths per year⁷.

Two options are identified in this respect:

- [Option 1](#) Provide further EU funding for, and encourage Member States and industry to fund, research regarding the fate, behaviour and impacts of pharmaceuticals in the environment
- [Option 2](#) Provide EU funding for, and encourage Member States and industry to fund, research on the role of antimicrobials/resistant microorganisms in the environment on the emergence and spread of antimicrobial resistance (AMR) and its link with human and animal health

Design

Designing “greener” substances

Because of the demonstrated risks of some pharmaceuticals on the environment, and in accordance with the precautionary principle, a number of scientists are:

- involved in developing molecules with reduced intrinsic environmentally hazardous properties; or
- exploring how to minimise their impacts on the environment by optimising administration modes (patches, cream, pills, etc.).

Perhaps because of concern that it might be costly and technically challenging, the concept of Benign-by-Design has not been significantly tested by the industry.

- [Option 3](#) Develop information resources and EU/industry co-funding initiatives to promote the design of active pharmaceutical ingredients (APIs) that pose lower risks to the environment

⁶ <http://www.ecdc.europa.eu/>

⁷ O'Neill (2014) *Antimicrobial resistance: Tackling a crisis for the health and wealth of nations*. The Review on Antimicrobial Resistance

Authorisation

Ensuring the scientific robustness, consistency and transparency of risk assessments

Since 2005 for veterinary pharmaceuticals (also called veterinary medicinal products or VMPs) and 2006 for human pharmaceuticals (also called human medicinal products or HMPs), the key regulatory instrument influencing the presence of pharmaceuticals in the environment has been the current framework for Environmental Risk Assessment (ERA), which is a part of the marketing authorisation (MA) process for pharmaceuticals for both human and veterinary use. It is described in specific European Medicines Agency (EMA) guidelines for human and veterinary pharmaceuticals.

ERA performed by applicants are reviewed by national medicines or environment agencies and/or the Scientific Committees of the EMA, depending on the selected authorisation procedure (centralised, decentralised, mutual recognition). Environmental experts are not always considered to be adequately involved in this review, in particular for HMPs, and a forum for harmonisation of assessments is missing.

Access to environmental datasets produced in the context of ERA is generally limited to risk assessors for confidentiality reasons, which explains the absence of publicly available datasets or their partial publication. When published, the quantity and quality of disclosed information vary depending on a number of factors and the information is difficult to find on the web sites of the respective agencies.

ERA provides valuable data to assess environmental risks for each pharmaceutical for which a MA is sought. Pharmaceuticals assessed as “posing a significant risk” to the environment at the time of the assessment can be placed on the market provided Risk Mitigation Measures (RMMs) are identified and/or implemented. However, although ERA results are taken into account in the overall benefit/risk analysis for a MA application in the case of VMPs, there is no such consideration with regard to the final outcome of the authorisation process for HMPs.

Furthermore, the capacity of ERA to capture risks related to Persistent Bio-accumulative and Toxic substances (PBT) and endocrine disruptors is questioned and detailed guidance on how to deal with substances other than the active pharmaceutical ingredients (API) itself (metabolites, excipients, degradation products) is missing.

The following options are aimed at tackling the aforementioned shortcomings:

- [Option 4](#) Strengthen the environmental expertise of the European Medicines Agency (EMA, its scientific committees) and the national competent authorities
- [Option 5](#) Ensure that all environmentally relevant toxicological thresholds for pharmaceuticals placed on the market are systematically made publicly available in a standardised format
- [Option 6](#) Develop a system for sharing comprehensive active-substance-based Environmental Risk Assessments (ERAs) at EU level
- [Option 7](#) Ensure that ERA results are systematically considered in the overall benefit/risk analysis for the authorisation of HMPs
- [Option 8](#) Ensure that ERAs adequately consider Persistent Bio-accumulative and Toxic substances (PBT) and endocrine properties for the APIs, as well as the toxicity and other properties of major metabolites, degradation products and excipients: a) for human pharmaceuticals, b) for veterinary pharmaceuticals.

Manufacturing

Promoting greener manufacturing processes

The discovery, in EU MS, of several hotspots of contamination downstream of pharmaceutical manufacturing facilities has increasingly raised concern about the emissions of pharmaceuticals at the manufacturing stage. The global impact of EU consumption of pharmaceuticals is also highlighted, as many pharmaceuticals are imported, and even EU-based pharmaceutical companies are increasingly outsourcing the manufacturing of pharmaceuticals to multiple suppliers in third countries. Many of these third countries are known to face critical pollution from bulk drug manufacturing⁸. Several voluntary initiatives from the industry indicate that practices can be improved to reduce emissions in the EU and/or along the global supply chain.

Nonetheless, existing EU instruments appear insufficient to properly regulate the emissions:

- The Industrial Emissions Directive (IED, 2010/75/EU), which applies to pharmaceutical manufacturing sites among others, does not include APIs in the list of polluting substances;
- APIs and excipients are subject to the REACH Regulation (Registration, Evaluation, Authorisation and restriction of Chemicals) but are exempt from REACH if they are already registered with the European Medicines Agency (EMA) as an ingredient of a medicinal product for human or veterinary use⁹;
- Guidelines for good manufacturing practices (GMP)¹⁰ essentially focus on quality and safety parameters and do not include any reference to potential impacts and risks of these practices on the environment.

There is a need to monitor and better control emissions from the pharmaceutical manufacturing sector in the EU and to increase transparency with regard to practices in the supply chain. The following options could potentially contribute to this objective:

- [Option 9](#) Under the Industrial Emissions Directive, review and revise Best Available Techniques Reference (BREF) documents relevant to emissions from the manufacturing of pharmaceuticals
- [Option 10](#) Prepare a sectoral reference document under the European Eco-Management and Audit Scheme (EMAS) to promote increased adoption by pharmaceutical companies, and by their global suppliers, of good environmental manufacturing standards
- [Option 11](#) Ensure that EU Good Manufacturing Practices (GMP) address discharges of active pharmaceutical ingredients (APIs), degradation products and excipients into the environment

⁸ Changing Markets/Ecostorm for Nordea (2016) Impacts of pharmaceutical pollution on communities and environment in India. <https://www.nordea.com/Images/35-107206/impacts%201-20.pdf>

Changing Markets/Ecostorm (2016) Superbugs in the Supply Chain. http://epha.org/wp-content/uploads/2016/10/Superbugsinthesupplychain_CMreport.pdf

Larsson, J. (2014) Pollution from drug manufacturing: review and perspectives. Royal Society Publishing. Published 13 October 2014. DOI: 10.1098/rstb.2013.0571

[Royal Society of Chemistry website, Jia H. \(2011\) Pharma pollution is out of control in China. www.rsc.org/chemistryworld/News/2011/June/24061103.asp](http://www.rsc.org/chemistryworld/News/2011/June/24061103.asp)

Reuters (2016) The cost of cheap drugs? Toxic Indian lake is 'superbug hotspot'. Reuters. [Politics Special Reports](http://www.reuters.com/article/us-health-superbugs-india-insight-idUSKCN11Y35G) | Thu Sep 29, 2016. <http://www.reuters.com/article/us-health-superbugs-india-insight-idUSKCN11Y35G>

⁹ Only transported isolated intermediates, starting materials and reagents are subject to REACH and require registration, evaluation or/and authorisation (in the last two cases)

¹⁰ These must be respected to obtain authorisations for the manufacturing or importation of medicinal products under the legislation for pharmaceuticals, as laid down in Commission Directive 91/356/EEC

Post-authorisation

Ensuring environmental risks are adequately taken into account and dealt with by mitigation actions where relevant

As mentioned in the section on authorisation, MA procedures take into account the conclusions of ERAs differently for HMPs and VMPs. Furthermore, for most pharmaceuticals placed on the market before 2005 and 2006, i.e. before ERA was required by the legislation for VMPs and HMPs, environmental considerations were not taken into account in the MA.

Several ERA dossiers remain incomplete because of the limited scientific knowledge at the time of the assessment or because MA has been granted with "post-marketing commitments" for some HMPs. In the case of veterinary pharmaceuticals, it may also happen that an authorisation is granted even if the dossier is not complete because missing data are not necessarily considered as a serious concern. The current post-marketing pharmacovigilance mechanism for pharmaceuticals does not ensure update of the ERA dossier once marketing has begun. Furthermore, its effectiveness at identifying and linking environmental impacts not generally attributable to a single product, unless in specific cases of accidental spills, is debated.

The RMMs specified in the MA are not always implemented and followed-up in practice, nor defined in synergy with other environmental policies' objectives. A pitfall of the current system for RMMs is that obligations lie with the MA holder, who is obliged to insert the RMMs in the product literature, whereas the action is usually required by the veterinarian or animal owner.

Several studies have reported the use of some HMPs with risk quotients greater than one (i.e. where the ratio between the Predicted or Measured Environmental Concentration (PEC or MEC) and the Predicted No-effect Concentration (PNEC) is >1), including some commonly sold over-the-counter (OTC) medicines. Other studies have confirmed previous findings about critical adverse effects of some pharmaceuticals at concentrations encountered in the environment (e.g. diclofenac, xenoestrogens). This calls for policy action to make sure environmental risks are adequately taken into account.

The following options aim at tackling the aforementioned shortcomings:

- [Option 12](#) Instigate an Environmental Risk Assessment (ERA) catching-up procedure for relevant pharmaceuticals for which there is still no or only an incomplete ERA
- [Option 13](#) Require from the marketing authorisation holder (MAH) the update/revision of ERAs based on post-marketing monitoring data or newly published information
- [Option 14](#) Link the need for a prescription to supply/obtain human pharmaceuticals (HMPs) to the results of ERAs, and provide guidelines for the enforcement of existing similar provisions for veterinary pharmaceuticals (VMPs)
- [Option 15](#) Require Member States to designate the authority/authorities responsible at national level for the follow-up and reporting obligations linked to implementation of risk mitigation measures

Use

Ensuring environmental risks and impacts observed post-marketing are identified and reported

The surveillance of environmental issues at post-marketing stage, or "eco-pharmacovigilance", is key to addressing the potential impacts of pharmaceuticals once in the environment and to ensuring that the predicted risk at the authorisation stage matches environmental data. In practice, these activities often remain informal, in particular for HMPs,

unlike the well-established pharmacovigilance systems for quality and patient/animal safety. Except for the six substances included in the surface water Watch list under the Water Framework Directive (WFD)¹¹, there is no EU-wide targeted monitoring of pharmaceuticals in surface and ground waters. Overall, information exchange and collaboration between human health, veterinary and environmental competent authorities remain limited.

This calls for considering options to ensure that new knowledge generated through research and environmental monitoring can be used to refine ERA conclusions where relevant:

Option 16 Establish routine dialogue and information exchange between relevant Member State agencies and authorities to help ensure that API levels in the environment are safe for the environment and human and animal health

Option 17 Ensure that environmental issues are a) introduced into the pharmacovigilance system for human pharmaceuticals (HMPs) and b) strengthened for veterinary pharmaceuticals (VMs), particularly in relation to AMR

Option 18 Include pharmaceuticals as relevant in the watch lists for monitoring surface and groundwater under the Water Framework Directive (WFD) a) along with AMR in relevant microorganisms when antimicrobials are included; b) without requiring monitoring of AMR

Promoting sustainable use of pharmaceuticals

Consumption patterns depend on several factors beyond therapeutic needs, such as prescriptions by doctors and veterinarians, patients' discontinuation of treatments¹², and increased prevalence and ability of patients to auto-medicate without professional advice¹³. In the last case, pharmacists, as the primary pharmaceutical retailers in the EU, may have a large influence on households' consumption patterns of OTC pharmaceuticals, which can contain substances posing a potential risk to the environment (e.g. – depending upon the country - diclofenac, antimicrobials).

Being in direct contact with patients or people in charge of medical/veterinary care, doctors, veterinarians and pharmacists have a key responsibility to inform patients about the correct use of pharmaceuticals, in particular in the context of increased concern with regard to AMR. Already in 1991, Rutten et al. observed: "Professional medical advice impacts patients' perceptions and attitude towards their illness and perceived need for antimicrobials, in particular when they are advised on what to expect in the course of the illness, including the realistic recovery time and self-management strategies"¹⁴.

Experience demonstrates that properly informing doctors, veterinarians, pharmacists and patients may contribute efficiently to the modification of procurement and consumption practices, and thus to a decrease in the release of pharmaceuticals into the environment. It also has significant benefits for the appropriate disposal of unused pharmaceuticals by households.

The three following options aim to promote more sustainable use of pharmaceuticals. They complement [Option 14](#) which proposes better consideration of environmental risks in the decision to sell a pharmaceutical OTC or solely under prescription.

¹¹ [Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for the Community action in the field of water policy](#)

¹² Non-negligible to large amounts (up to 50% in some MS) of purchased medicinal products end up unused/outdated because of treatment interruptions (mostly due to intolerance to the initial medicine and voluntary discontinuation)

¹³ Although the price of pharmaceuticals and reimbursement schemes are also factors that may influence medicinal-product consumption, they remain under full Member States' competence and responsibility. They are part of social and health policy, but not perceived as the most relevant factors in reaching environmental objectives.

¹⁴ Rutten G, Van Eijk J, Beek M, Van der Velden H. (1991) Patient education about cough: effect on the consulting behaviour of general practice patients. *Br J Gen Pract*; 41:289-92.

[Option 19](#) Encourage Member States to increase the consideration of environmental aspects during medical/veterinary education and advanced training of healthcare professionals including healthcare managers

[Option 20](#) Ensure the provision of information to the general public that encourages the sustainable use of pharmaceuticals, in particular antimicrobials

[Option 21](#) Develop recommendations or requirements regarding the size and form of packaging for pharmaceuticals to facilitate their efficient use

Waste collection and disposal

Ensuring appropriate collection and disposal of unused pharmaceuticals and pharmaceutical waste

The use of pharmaceuticals produces two major waste streams:

- Unused pharmaceuticals, which are generally disposed of along with municipal waste or directly into sewage systems;
- Pharmaceutical residues naturally excreted by patients or animals after use and contained in effluents of e.g. farms, hospitals, or households. This is dealt with in the next section "Wastewater collection, treatment and reuse".

In the case of unused pharmaceuticals - since 2004 for HMPs, and since 2001 for VMPs - all EU MS have been required to provide collection systems in order to better regulate disposal practices. Some EU MS implement these schemes through an extended producer responsibility. However, in 2010, a large proportion of unused medicinal products were still not collected or returned to pharmacies in the majority of EU MS, because of heterogeneous implementation of collection systems, limited disposal and collection points and a lack of awareness among the general public. According to a recent study, the loss due to unused prescribed pharmaceuticals in the UK alone was estimated to be £300 million a year¹⁵.

Most pharmaceuticals are not considered as hazardous substances¹⁶ under the Regulation on Classification, Labelling and Packaging of substances and mixtures (CLP)¹⁷ or the list of Waste¹⁸ and hence do not require specific waste management beyond collection and incineration.

The following options aim to contribute to more appropriate collection and disposal of unused pharmaceutical products and pharmaceutical waste.

[Option 22](#) Promote better enforcement of EU legislation with regard to the implementation of waste collection schemes for human and veterinary pharmaceuticals, including through extended producer responsibility

[Option 23](#) Ensure that the CLP Regulation does not exclude pharmaceuticals in medicinal products, and that its provisions are consistent with the Waste Framework Directive

¹⁵ York Health Economics Consortium, 2010

¹⁶ Except for Cytotoxic and cytostatic (anti-cancer) pharmaceuticals classified as hazardous waste under the Waste Framework Directive, and which require specific management

¹⁷ Regulation (EC) No 1272/2008, OJ L 353

¹⁸ Commission Decision 2014/955/EU on the list of Waste

Waste water treatment and reuse

Promoting more effective treatment of waste water, manure and sludge

Some pharmaceuticals are regularly detected in effluents from waste water treatment plants, and the presence of pharmaceuticals including antimicrobials and AMR microorganisms in manure, sludge and reclaimed water used to amend or irrigate agricultural soils has raised particular concern with regard to their possible bioaccumulation in the trophic chain and the development and spread of AMR. Although Prosser et al. (2015)¹⁹ suggest on the basis of their assessment that "*the majority of individual PPCPs in the edible tissue of plants due to biosolids or manure amendment or wastewater irrigation represent a de minimis risk to human health*", further risk characterisation should be conducted to better understand the risks – in particular from mixtures - to health and the environment, including from the use of reclaimed water in comparison with other sources of water for irrigation.

The effectiveness of standard water treatment to remove pharmaceuticals and their residues from waste water remains highly variable, depending on the properties of the pharmaceutical, the waste water treatment process and initial concentrations in the influent. It should also be noted that water treatment is expensive (in terms of energy, materials, disposal of sludge), and not consistent with the aim of preventing pollution by tackling the source. In this respect, there is increasing interest in source separation (e.g. urine bags) and pre-treatment of effluents where relevant in hospitals and healthcare centres. Until now though, most initiatives have remained at pilot scale.

Advanced water treatments are widely discussed as one of the most promising options for the removal of pharmaceuticals entering the aquatic environment and may become key in preventing the spread of AMR in the next few years. They may be decisive in the capacity to use reclaimed water and sludge e.g. for irrigation and soil amendment. As implied above, these techniques require further optimisation and development for increased competitiveness.

The EU already provides several funding opportunities in the field of advanced water treatment, at the R&D or implementation stages, but the development of these new technologies remains limited in practice.

In the EU, the monitoring and removal of pharmaceutical substances is not specifically regulated (either at EU level by the Urban Waste water Treatment Directive (UWWTD) or the IED, nor at Member-State level, except in very few countries such as the UK). Nor do current policy instruments specifically tackle the issue of pharmaceuticals in irrigation water, sludge or manure (IED, Sewage Sludge Directive, Fertiliser Regulation, and agricultural policies such as the Nitrates Directive and the CAP). On the other hand, several Member States already forbid the reuse of sewage sludge in agricultural fields based on the precautionary principle.

The following options could contribute to more effective treatment of waste water and opportunities to reuse sludge, manure and wastewater for agricultural purposes:

- [Option 24](#) Establish EU guidelines for appropriate wastewater management in hospitals and healthcare centres
- [Option 25](#) Require monitoring of antimicrobials and AMR microorganisms in the effluent and organic waste from potential "hotspots" such as large waste water treatment plants, hospitals, pharmaceutical manufacturing sites and intensive livestock farms
- [Option 26](#) Develop EU funding opportunities for research, development and implementation of advanced water treatment technologies to ensure that levels of pharmaceuticals, including antibiotics, and of AMR microorganisms,

¹⁹ Prosser et al. (2015). Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation. *Environment international*, 75, 223-233 (including corrigendum).

are reduced

[Option 27](#) Encourage Member States to establish innovative mechanisms for investing in advanced (waste and drinking) water treatment

[Option 28](#) Take additional measures, e.g. set quality standards or risk assessment requirements, to ensure that the concentrations of relevant pharmaceuticals and AMR microorganisms in manure, sewage sludge, and irrigation water are safe before it can be spread on agricultural fields

[Option 29](#) Encourage Member States to revise their Codes of Good Agricultural Practice and revise relevant best available techniques under the IED at EU level to include provisions for the handling of manure containing pharmaceuticals/AMR microorganisms

Whole life-cycle: overall management

Promoting better overall management of pharmaceutical emissions into soils and the aquatic environment

Several EU Member States and neighbouring countries have already taken action towards better protection of water resources from pharmaceuticals, either specifically (e.g. in Sweden and France) or as part of a larger strategy on micropollutants (e.g. in Switzerland). These initiatives provide a source of inspiration for other Member States for the development of concrete measures to better manage pollution by pharmaceuticals at national and river basin level. Guidance could be developed in the framework of the Common Implementation Strategy for the Water Framework Directive (WFD) bringing together the best practices and advice to enable water managers to improve their planning and measures. The guidance could emphasise the need to consider emissions from the whole lifecycle, and the contribution many measures could make to resource efficiency and the circular economy.

[Option 30](#) Prepare guidance under the Common Implementation Strategy (CIS) for the Water Framework Directive (WFD) to support better Member State action against pharmaceuticals in the aquatic environment

Factsheets

Objective	Improved understanding of the risks from pharmaceuticals to the environment		
Option 1: Provide further EU funding for, and encourage Member States and industry to fund, research regarding the fate, behaviour and impacts of pharmaceuticals in the environment			
Context			
<ul style="list-style-type: none"> • The EU has funded several research projects on pharmaceuticals in the environment, and these have contributed to the growing body of information on their presence and effects, information underlying the decision to develop an EU strategic approach to pharmaceuticals in the environment. • However, information regarding environmental risks is still not sufficient for the majority of pharmaceuticals currently on the EU market, either because of limited knowledge of environmental occurrence or because of insufficient publicly available data on the ecotoxicology of many pharmaceuticals. Data often remain scattered in individual study reports, heterogeneous, incomplete and difficult to access at EU level. • Fostering research activities to synthesise data from different studies, and to identify and fill data gaps, and fostering collaboration between public and private entities, should enable additional knowledge to be gained on the issue of the occurrence, fate and impacts of pharmaceuticals. Existing research results are critical to the development of the EU strategic approach to pharmaceuticals in the environment and additional research will further benefit its follow up. 			
Description			
<p>This option would involve developing research activities within the Horizon 2020 research program and in cooperation with EU MS and industry, in order to identify and prioritise the main risks posed by pharmaceuticals to the environment and to support policy actions accordingly. The following research fields could be addressed (non-exhaustive list): environmental concentrations and fate, ecotoxicity (chronic toxicity, assessment of endocrine-disruptive properties, effects of metabolites and degradation products, mixture effects), bioaccumulation in plants and animals, and health effects on vulnerable populations via the environment.</p>			
Preliminary assessment			
Strengths	Weaknesses		
<ul style="list-style-type: none"> • EU scientific community already active on this topic, relevant synergies can be exploited and data gaps overcome 	<ul style="list-style-type: none"> • Long time scale needed for scientific research 		
Opportunities	Threats		
<ul style="list-style-type: none"> • Synergies with other EU and national research programs • Sustainable development among industrial stakeholders: involvement in public-private research may be an asset for competitiveness 	<ul style="list-style-type: none"> • Resources needed (human and technical equipment) and costs associated • Difficulty and delays in translating research results into action • Potential lack of harmonisation and consensus regarding assessment/monitoring techniques 		
Further information			
<p>In the framework of this option, several publications highlight research needs with regard to pharmaceuticals in the environment. A few examples are provided in the reference list below.</p>			

Recent EU research projects that have investigated the issue include:

- KNAPPE: *Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters*. FP6 project. <http://ecologic.eu/2293>. Final report, 2008: http://cordis.europa.eu/docs/publications/1245/124584761-6_en.pdf
- PHARMAS: FP7 project. <http://www.pharmas-eu.net/>
- Cytothreat: FP7 project. <http://www.cytothreat.eu/>
- PILLS: an INTERREG IV B project running from 2007 to 2012. <http://www.pills-project.eu/>
- No Pills in Water: an Interreg IV B NWE project partnership running from 2012 to 2015. <http://www.no-pills.eu/?lang=fr> Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE), running from 2015 to 2018. <http://i-pie.org/>.

The EU is also co-funding, with industry, the initiative "Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE)" which aims to establish a framework that uses information from toxicological studies, pharmacological mode of action and in silico models to support intelligence-based environmental testing of pharmaceuticals in development and to prioritise legacy pharmaceuticals (authorised prior to 2006). One of the expected outcomes is a high-quality database on properties, environmental fate characteristics and ecotoxicity of APIs (ECT, 2015).

Selected references

Stakeholder consultation

Caldwell, D., Mastrocco, F., Margiotta-Casaluci, L., & Brooks, B. (2014). *An integrated approach for prioritising pharmaceuticals found in the environment for risk assessment, monitoring and advanced research*. *Chemosphere*.

Nica, V., Menaballi, L., Azimonti, G., & Finizio, A. (2014). *RANKVET: A new ranking method for comparing and prioritising the environmental risk of veterinary pharmaceuticals*. *Ecological Indicators*, 270-276.

Orias, F., & Yves, P. (2013). *Pharmaceuticals in hospital wastewater: their ecotoxicity and contribution to the environmental hazard to the effluent*. *Chemosphere*.

Rand-Weaver, M. (2013). *The read-across hypothesis and environmental risk assessment of pharmaceuticals*. *Environ. Sci. Technol*, 11384–11395.

Roos (2012). *Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection*. *Sci. Total Environ*, 102-110.

Shore, R. (2014). *Detection and drivers of exposure and effects of pharmaceuticals in higher vertebrates*. *Phil.Trans. R. Soc. B*, 20130570.

Silva, B. (2015). *Pharmaceuticals in the Environment: Pharmaceuticals in the Environment Case Study of Psychiatric Drugs*. In B. Silva et al., *Psychiatric Pharmaceuticals as Emerging Contaminants in Wastewater* (pp. 19-46). SpringerBriefs in Green Chemistry for Sustainability.

Objective	Improved understanding of the risks from pharmaceuticals to the environment	
Option 2: Provide further EU funding for, and encourage Member States and industry to fund, research on the role of antimicrobials/resistant microorganisms in the environment in the emergence and spread of antimicrobial resistance (AMR) and its link with human and animal health		
Context		
<ul style="list-style-type: none"> • The development and spread of AMR is being accelerated by excessive use of antimicrobial medicines, discontinuation of treatments, inadequate or non-existent programmes for infection prevention and control, poor-quality medicines, weak laboratory capacity, inadequate surveillance and insufficient regulation of the use of antimicrobial medicines. • Singled out as one of the global public health issues of great concern, AMR has received increasing attention in the past few years. However, there is still no monitoring or regulation of the release of antimicrobials or resistant genetic determinants (resistant microorganisms) into the environment, e.g. through wastewater systems or manure spread on the fields. • Further research is needed to understand better the relationship between the release of antimicrobials in the environment, wastewater treatment/manure spreading, development and spread of resistance within the environment and the consequences for animal and human health. More work is also needed to identify risk management options for reducing the spread of antimicrobial-resistance determinants via environmental pathways, and reducing the risks to human and animal health. 		
Description		
<p>This option would involve developing research activities within the Horizon 2020 research program and in cooperation with the industry, in order to:</p> <ul style="list-style-type: none"> • Further investigate the link between the release of antimicrobials/resistant microorganisms in the environment, the emergence and spread of AMR in the environment and the impact on animal and human health; • Explore possible solutions to reduce this spread and the potential risks to human and animal health; • Build on and develop synergies with the research initiatives launched in November 2011 in the context of the EU action plan against the rising threats from AMR. 		
Preliminary assessment		
Strengths <ul style="list-style-type: none"> • EU scientific community already active on this topic, relevant synergies can be exploited and data gaps overcome 	Weaknesses <ul style="list-style-type: none"> • Long time scale for scientific research • AMR is a global issue requiring global cooperation 	
Opportunities <ul style="list-style-type: none"> • Possibility to promote management solutions at no or little cost • Synergies with 2011 EU action plan against rising threats from AMR • Global issue 	Threats <ul style="list-style-type: none"> • Resources needed (human, technical equipment) and costs associated • Emerging research field, with uncertainty regarding risk and metrics to measure spread of AMR and related risk • Difficulty and delay in translating research results into action. 	
Further information		
<p>In the framework of this option, several publications highlight current research needs with regard to antimicrobials and the development of resistance in the environment. The European Commission funds research projects on AMR through its Framework Programmes (FP) for research and innovation. This support started with FP5 in 1999 and continued through to FP7 and Horizon 2020 today.</p> <p>Several examples of EU-funded projects on AMR are summarised in the following EU publication:</p>		

https://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/pdf/eu-research-on-antimicrobial-resistance_en.pdf

Selected references

Stakeholder consultation

Ashbolt, N. (2013). *Human Health Risk Assessment (HHRA) for Environmental Development and Transfer of Antibiotic Resistance*. Environ Health Perspect, 993–1001.

Bell et al. (2014). *A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance*. MC Infectious Diseases 14:13.

Berendonk, T. (2015). *Tackling antibiotic resistance: the environmental framework*. Nature Reviews Microbiology, 1-8.

Berkner et al. (2014). *Antibiotic resistance and the environment —there and back again*. Science & Society series on Science and Drugs, 1-5

CDC website: <http://www.cdc.gov/drugresistance/about.html>

European Commission (2011). *EU Research on Antimicrobial Resistance*. EU projects 2007-2010. https://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/pdf/eu-research-on-antimicrobial-resistance_en.pdf

Finley, R. (2013). *The Scourge of Antibiotic Resistance: The Important Role of the Environment*. Clinical Infectious Diseases Advance, 1-7.

Jechalke, S. (2014). *Fate and effects of veterinary antibiotics in soil*. Trends in Microbiology, 536-545.

Marti. (2014). *The role of aquatic ecosystems as reservoirs of antibiotic resistance*. Trends in Microbiology, 36-42.

Port, J. (2014). *Metagenomic Frameworks for Monitoring Antibiotic Resistance in Aquatic Environments*. Environ Health Perspect, 222–228.

Pruden, A. (2013). *Management Options for Reducing the Release of Antibiotics and Antibiotic Resistance Genes to the Environment*. Environ Health Perspect, 878–885.

Knapp, C. (2010). *Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940*. Environ Sci Technol, 580-587

Singer, R. (2014). *Human health impacts of antibiotic use in agriculture: A push for improved causal inference*. Current Opinion in Microbiology, 1–8.

UK House of Parliament. (2013). *Antimicrobial resistance*. <http://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2010/antimicrobial-resistance-amr/>

Wellington, E. (2013). *The role of the natural environment in the emergence of antibiotic resistance in gram-negative bacteria*. Lancet Infect Dis , 155–165.

WHO. (2014a). *Antimicrobial resistance: global report on surveillance*.

Williams-Nguyen, J. (2016). *Antibiotics and Antibiotic Resistance in Agroecosystems: State of the Science*. Journal of Environmental Quality, 394-406.

Wright, G. (2010). *Antibiotic resistance in the environment: a link to the clinic? Current Opinion in Microbiology*, 589–594

Objective		Designing "greener" substances	
Option 3: Develop information resources and EU/industry co-funding initiatives to promote the design of active pharmaceutical ingredients (APIs) that pose lower risks to the environment			
Context			
<ul style="list-style-type: none"> • Current source-control and end-of-pipe measures are not always efficient at preventing persistent micro-pollutants from entering the environment. • This is why the concept of Sustainable Pharmacy including Benign by Design aims to design pharmaceutical molecules that achieve the functionality needed for their use while reducing their inherent environmental hazard. • Derived from the larger field of Green Chemistry, this concept has not yet been put into practice in the pharmaceuticals arena. The process of developing therapies is costly, with many tests, which creates an incentive for manufacturers to invest in developing therapies which have a greater chance of success. Green design adds another criterion, amongst many others, to take into account in the R&D process. • There is still very limited collaboration in this respect between the scientific community and the industry. 			
Description			
<p>This option aims at developing guidelines to encourage the design of pharmaceuticals which pose lower risks to the environment, based on first examples and methodologies. These guidelines would present methods to design new molecules or re-design existing ones and could be accompanied by incentives e.g. in the form of further research and development funding encouraging collaboration between research communities, the pharmaceutical industry and wastewater treatment sector.</p>			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> • Reduced ecotoxicity and exposure through improved environmental biodegradability • Innovative approach which provides new perspectives for the future • Existing scientific background available to drive the development of guidelines 		<ul style="list-style-type: none"> • Possibly limited technical applicability based on current knowledge, because limited to simple chemical structures • Data-intensive: data about the biodegradability of different chemical structures not always available 	
Opportunities		Threats	
<ul style="list-style-type: none"> • Reduced need for advanced water treatment for removal • Business opportunities: market development for more environmentally-friendly pharmaceuticals, reduction of the administrative burden associated with a full ERA • Builds on industry support for green chemistry • New scientific developments and synergies with pharmacological objectives 		<ul style="list-style-type: none"> • Additional time and resources for R&D • Longer time-to-market, with a reduced time for market exclusivity from innovating companies • Requires the definition of criteria for "green" pharmaceuticals and/or a conventional baseline to be able to assess "greener" pharmaceuticals • Risk of being unsuccessful at maintaining the therapeutic effects over time, cf the comparable existing API • Specific requirements for formulation and storage to counter decreased stability 	

Further Information

The scientific background for targeted and non-targeted strategies already exists: this can be used for the development of guidelines. In the late 1990's – early 2000's, first promising evidence was found that the goal to combine pharmaceutical development with environmental considerations is feasible by re-structuring the cancer drugs ifosfamide and 5-fluorouracil. The alternative molecules possess improved biodegradability while retaining and even improving the pharmacological properties. The drug candidate glufosphamide is currently in late stage clinical development, whereas cytarabine and gemcitabine have been in use for decades (Leder, Rastogi, & Kümmerer, 2015). Rastogi et al. investigated the possibility to re-design beta-blockers, such as propranolol, metoprolol and atenolol into biodegradable alternatives (although the pharmacological potency of atenolol is to be further investigated).

Examples from industry also show that there is interest in investigating further such options: there may be some synergies with the natural pharmacological objectives to deliver improved patient benefit. For instance, the Drug Design Criteria "100% Oral absorption", "Metabolised in patient to inert substances", and "Effective in all patients treated" would contribute to reduce pollution at the source. The Drug Design Criteria "Disease receptor specific" and "No effects other than therapeutic ones" would lead to lower potential impact of the residual active material on ecosystems (Taylor, 2015).

Example of political support: In 2012, the German Federal Environmental Foundation (DBU) announced a grant initiative on the subject of "Sustainable Pharmacy" for small and medium-sized businesses and research institutions (DBU, 2012). This initiative, which targeted projects addressing the principles of green chemistry, was quite successful, but lessons learnt from implementation of projects in this context show more efforts on conservation of resources and efficient production rather than on the green design of molecules (IFAT, 2016).

Selected references

Stakeholder consultation

Anastas, P. T. & Warner, J. C. (1998). *Green Chemistry: Theory and Practice*. New York: Oxford University Press.

DBU (2012, June). DBU aktuell Nr. 6 | June 2012. Retrieved from https://www.dbu.de/2673ibook68322_33123_2538.html

IFAT (2016, March). *Focus on sustainable pharmacy*. Retrieved from

<http://www.ifat.de/media/website/files/pdf/industries/nachhaltige-pharmazie-im-fokus.pdf>

Kümmerer, K. (2016). *Benign by Design*. In H. F. Louise Summerton, *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*. (p. Chapter 7). Royal Society of Chemistry.

Leder, C. Rastogi, T., & Kümmerer, K. (2015). *Putting benign by design into practice - novel concepts for green and sustainable pharmacy: Designing green drug derivatives by non-targeted synthesis and screening for biodegradability*. *Sustainable Chemistry and Pharmacy*, 31–36.

Lubick, N. (2008). *Opening the "green pharmacy"*. *Environ. Sci. Technol* 42, 5620-5621.

Rastogi, T., Leder, C., & Kümmerer, K. (2014). *Designing green derivatives of β -blocker Metoprolol: a tiered approach for green and sustainable pharmacy and chemistry*. *Chemosphere*.

Rastogi, T., Leder, C., & Kümmerer, K. (2015a). *Re-Designing of Existing Pharmaceuticals for Environmental Biodegradability: A Tiered Approach with β Blocker Propranolol as an Example*. *Environmental Science and Technology*, 49, 11756–11763.

Rastogi, T., Leder, C., & Kümmerer, K. (2015b). *A sustainable chemistry solution to the presence of pharmaceuticals and chemicals in the aquatic environment – the example of re-designing β -blocker Atenolol*. *RSC Advances*.

Straub, J. O. (2010). *Protein and Peptide Therapeutics: An Example of "Benign by Nature" Active Pharmaceutical Ingredients*. In *Green and Sustainable Pharmacy* (pp. pp 127-133). Springer Berlin Heidelberg.

Taylor, D. (2015). *The Pharmaceutical Industry and the Future of Drug Development. In Issues in Environmental Science and Technology*. Royal Society of Chemistry.

Objective	Ensuring the scientific robustness, consistency and transparency of environmental risk assessments
Option 4: Strengthen the environmental expertise of the European Medicines Agency (EMA, its scientific committees) and the national competent authorities	
Context	
<ul style="list-style-type: none"> • At EU level, the Committees for Medicinal Products for Veterinary Use (CVMP) and for Human Use (CHMP) play a key role in the marketing authorisation (MA) of pharmaceuticals, development of guidelines and harmonisation of requirements²⁰. The CVMP and CHMP are composed by experts nominated by the EU MS in consultation with the EMA’s Management Board: <ul style="list-style-type: none"> - For veterinary pharmaceuticals, one CVMP member of about 30 is an expert in environmental risk assessment (this member is one of the up to five co-opted members recruited to provide additional expertise in a particular scientific area). The CVMP is moreover supported by the work of the ERA Working Party (ERA WP), which consists of 10 experts with expertise in ecotoxicology (environmental fate and degradation), general toxicology, ecology and environmental risk assessment. The ERA WP receives a mandate to work on guidelines and reflection papers etc. However, the ERA WP is involved neither in the authorisation of VMs, nor when a “referral” is initiated because of environmental risks. - For human pharmaceuticals, there is currently no declared expert for environmental assessment or specific representative of environmental issues in the CHMP. A complementary ERA Working Party such as that for veterinary pharmaceuticals is missing. The Safety Working Party (SWP) provides recommendations to the CHMP on all matters relating directly or indirectly to non-clinical aspects of safety. This group is involved, in an ad-hoc (i.e. not permanent) manner, in the revision of ERA guidelines for HMPs, along with ERA experts from medicines agencies and environmental agencies. • At national level, medicines agencies are in charge of reviewing MA dossiers and therefore the ERAs. Depending on the EU MS, environmental experts are not always involved in this review. 	
Description	
<p>This option aims to strengthen the standards for environmental evaluation and expertise and encourage scientific committees via the following actions:</p> <ul style="list-style-type: none"> • Nominate environmental experts for CHMP and national medicines agencies for the review of ERAs and other environmental issues in MA; • Establish an ERA working party to support CHMP with the ERAs; • For both veterinary and human pharmaceuticals, provide guidance and training to ERA dossier assessors to improve the assessment of completeness and quality of ERAs in the different EU MS and to CVMP and CHMP to better consider the outcomes in the risk-benefit analysis. A meeting of environmental risk assessors could be organised once a year to harmonise the assessments, on top of the three meetings of the ERA WP for VMs. 	

²⁰ They are responsible for:

- in centralised procedures, initial assessment of medicines for which an EU-wide MA is sought and of post-authorisation activities, including for which an EU-wide MA is sought;
- in the ‘mutual-recognition’ and ‘decentralised’ procedures, arbitrating between Member States in cases where there is a disagreement concerning the MA. They also act in referral cases, when there are concerns relating to the protection of public health or where other Community interests are at stake;
- providing assistance to companies researching and developing new veterinary medicines;
- preparing scientific and regulatory guidelines for the veterinary pharmaceuticals industry;
- ensuring cooperation with international partners on the harmonisation of regulatory requirements for veterinary medicines.

Preliminary assessment	
<p>Strengths</p> <ul style="list-style-type: none"> • Environmental issues can be addressed consistently across EU MS • Knowledge capitalisation on ERA procedures and best practices in MS. • Successful examples of integration of environmental experts at national level and in CVMP, and collaboration between SWP and environmental agencies. 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Limitation on the number of members per Committee: CHMP currently has a limit of 5 co-opted members; current members already cover key topics.
<p>Opportunities</p> <ul style="list-style-type: none"> • Information sharing would reduce administrative costs in EU MS • Identification at an early stage of environmental risks and challenges to be tackled 	<p>Threats</p> <ul style="list-style-type: none"> • Risk of limited and heterogeneous implementation across EU MS and scientific committees • Costs and selection process of new experts and resources needed for the organisation of the workshop
Further information	
<p>The review of ERA conducted by national authorities could take inspiration from the functioning of the REACH regulatory Committee composed of representatives from MS supporting the Commission on test methods. The Environmental Risk Assessment Working Party within the European Medicines Agency, which provides advice to the CVMP, could be an example for the CHMP.</p> <p>Currently, the preparation of a revised ERA guideline for HMPs involves the Safety Working Party of the CHMP and three specialised ERA assessors from EU National medicines agencies and environmental agencies (CHMP, 2016). This group is an ad-hoc Working group, not intended to become permanent.</p>	
Selected references	
<p>Stakeholder consultation http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000262.jsp&mid=WC0b01ac0580028dd8</p> <p>Current members and alternates of the Committee for Medicinal Products for Human Use (CHMP): http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000002.jsp&mid=WC0b01ac0580028c7c</p> <p>Safety Working Party: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000021.jsp&mid=WC0b01ac0580028d93</p> <p>Current members and alternates of the Committee for Medicinal Products for Veterinary Use (CVMP): http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000003.jsp&mid=WC0b01ac0580028e0f</p> <p>Environmental Risk Assessment Working Party within the CVMP: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CVMP/people_listing_000037.jsp&mid=WC0b01ac0580028e2b</p> <p><u>CHMP (2016) Concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/4447/00 corr 2)</u></p>	

Objective	Ensuring the scientific robustness, consistency and transparency of environmental risk assessments	
Option 5: Ensure that all environmentally relevant toxicological thresholds for pharmaceuticals placed on the market are systematically made publicly available in a standardised format		
Context		
<ul style="list-style-type: none"> • A public assessment report must be published for each marketed pharmaceutical product. In a centralised procedure (where an EU-wide marketing authorisation is sought), a European Public Assessment Report (EPAR) is published by the European Medicines Agency (EMA). In decentralised and mutual recognition procedures (where an authorisation is sought by specific Member State(s)), a national Public Assessment Report (PAR) is published by the competent authorities of the relevant Member States. • These reports must contain a summary of the characteristics of active substances in a format and language that is understandable to the general public²¹. • However, the reporting of environmental data (including ecotoxicological data, e.g. PNEC data for surface water, groundwater and soil, and the overall risk ratio)) and ERA results is not consistent in these reports. • Although some (E)PARs include environmental information in a chapter called Ecotoxicology/Environmental Risk Assessment, the information remains generally incomplete and does not properly reflect all relevant environmental data (e.g. data limited to Phase I of the ERA) • The results of ERAs for different (E)PARs may also lack coherence and consistency. Even when published, the results may be difficult to find. Easy access requires knowledge of the name of the product containing the targeted substance as well as of the procedure for assessment (centralised, decentralised, or mutual recognition). 		
Description		
<p>This option aims to:</p> <ul style="list-style-type: none"> • develop a harmonised template for EPARs and PARs, including the display of environmental information; <ul style="list-style-type: none"> • require the publication of the main ERA results (at least the PEC and the rational for not going through Phase II testing when not done) and of environmentally relevant toxicological thresholds (endpoints) for each API; • centralise the environmental data reported in EPARs and PARs in an open access database per API, giving easy access to the general public to non-confidential information and highlighting market holders in charge of the tests (for further contact under option 6). 		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Better transparency of environmentally relevant information • Easier access to competent authorities involved in decisions related to environmental protection • Easier identification of inconsistencies between ERA results and endpoints • Can build on lessons learnt, e.g. from the compilation of data for chemicals in the ECHA database 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Confidentiality issues: endpoints alone cannot be used in an ERA. The possibility to build on ERA sections from a previous product would require specific agreements with regard to intellectual property rights for use of the original data 	

²¹ according to the Regulation for the supervision of medicinal products ((EC) 726/2004) and directives on medicinal products for human and veterinary use (2001/83/EC and 2001/82/EC)

<p>Opportunities</p> <ul style="list-style-type: none"> Themes included in the upcoming work program of the CHMP for the revision of ERA guidelines (CHMP, 2016) 	<p>Threats</p> <ul style="list-style-type: none"> Technical challenges for harmonisation of PARs and/or consolidation of data for every nationally authorised product In the case of a consolidated database: proportionality of costs in terms of human resources and IT for the EMA or the competent authorities in charge of the database, compared to expected benefits in terms of impacts on the environmental and public health Need for a catching-up procedure to make sure existing PARs present relevant environmental information
<p>Further information</p>	
<p>The CHMP recently highlighted in its concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/4447/00 corr 2) the need to review possibilities for better utilisation of data in the public domain to make a scientifically sound assessment of the environmental risk, with a special interest to avoid unnecessary repetition of animal studies (e.g. fish) (CHMP, 2016).</p> <p>In Sweden, the WikiPharma open-access database is an example of initiatives gathering environmental information to consolidate it in a database. It is an outcome of the research project "Swedish MistraPharma", which consolidates publicly available ecotoxicity data for pharmaceutical substances, focusing on HMPs available on the Swedish market. This database is intended to be continuously updated. However, most data collected is provided by the industry and not yet assessed independently by a competent authority. As such, so far, data from this database cannot be accepted in an ERA process. The EMA/EU data base would have to be administered by regulators to ensure that only valid, plausible, and relevant information are included. The current databases could however provide a template for how to organise this ERA data base.</p>	
<p>Selected references</p>	
<p><u>Legal ground:</u></p> <p>European Commission. (2003). <i>Directive 2003/4/EC of the European Parliament and of the Council of 28 January 2003 on public access to environmental information and repealing Council Directive 90/313/EEC</i></p> <p>Regulation on the supervision of medicinal products ((EC) 726/2004)</p> <p>Directives on medicinal products for human and veterinary use (2001/83/EC and 2001/82/EC)</p> <p><u>Other sources:</u></p> <p>Stakeholder consultation</p> <p>Ågerstrand, M. et al. (2015). <i>Improving environmental risk assessment of human pharmaceuticals</i>. Environmental science & technology, 49(9), pp. 5336-5345.</p> <p>Bio Intelligence Service (2013). <i>Study on the environmental risks of medicinal products</i>. Final report to the European Commission.</p> <p>Caneva L., B. M.-A.-M. (2014). <i>Critical review on the Environmental Risk Assessment of medicinal products for human use in the centralised procedure</i>.</p> <p>CHMP (2016) <u>CHMP (2016) Concept paper on the revision of the 'Guideline on the 4 environmental risk assessment of medicinal products for 5 human use' (EMA/CHMP/SWP/4447/00 corr 2)</u></p> <p>ECT (2015). <i>Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE)</i>. http://ect.de/ipie/</p> <p>http://ec.europa.eu/health/files/environment/study_environment.pdf</p> <p>Wiki Pharma open access database: http://www.mistrapharma.se/wikipharma-13497291</p>	

Objective	Ensuring the scientific robustness, consistency and transparency of risk assessments	
Option 6: Develop a system for sharing comprehensive active-substance-based Environmental Risk Assessments (ERAs) at EU level		
Context		
<ul style="list-style-type: none"> • The Marketing authorisation (MA), and consequently the outcome of the ERA, are based on the API that is contained in a pharmaceutical product. The amount of the API and/or dose may vary between pharmaceutical products resulting in different outcomes, although the hazard characterisation is substance based, which explains why ERA for a product is an obligation for the applicant. • Today, MA holders have difficulty sharing ERA results relating to hazard characterisation for a single API without a clear legal framework on Intellectual Property, which would allow existing assessments to be built upon and ensure their consistency. Furthermore, the absence of centralisation of information on pharmaceuticals containing the same API also hampers the consideration of additive effects due to the use of several pharmaceuticals containing the same API, in particular when predicting environmental concentrations. 		
Description		
<p>This option would promote the carrying out of an active-substance-based ERAs, which would involve the following elements:</p> <ul style="list-style-type: none"> • Documentation of a dossier under a substance-based approach: The consortium of companies using the same API (future marketing authorisation holders) would submit all relevant tests according to the CHMP or CVMP guidelines. This would consist of physico-chemical data, fate & effects data. These data would be stored in a non-public part of the database established in option 5. Where tests had been conducted previously on the same API in the context of previous authorisations, the consortium of companies could build on the previous data, subject to a clear Intellectual Property framework covering access to those data (also stored in the non-public part of the database). The existence of previous tests on the API could be identified through use of the public part of the database. The calculation of risk would still be required for each product, as exposure data (e.g. Predicted environmental concentrations - PEC) attributable to each would probably differ. • Product authorisation (use of data from the dossier): All applicants that are part of the consortium would have the right to use the list of endpoints for their product authorisations in order to derive the respective PNECs. New applicants would have to gain a letter of access from the consortium. Hazard characterisation could be covered as proposed above but given that exposure could be different, all other aspects of ERAs (calculation of risk quotients, determination of RMMs) would remain product-based. 		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Harmonisation of ERAs regarding hazard and risk characterisation for similar substances. • Resource efficiency savings by avoiding repetition of testing (animal welfare, fewer testing materials, etc.) • Coherence and complementarity with the current product-based assessment: products would still be assessed for exposure, and would refer to the relevant substance-based procedure for fate and effect data • Resources and time: although establishing such a procedure would be time consuming at first, it would save time and resources once it is up and running (fewer assessments will be needed) 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Work involved in establishing and maintaining database and ensuring quality control • Need for financial/legal agreements with regard to Intellectual Property rights between applicants for information sharing 	

<p>Opportunities</p> <ul style="list-style-type: none"> • Optimisation of resource use (including information sharing for future dossiers) by applicants and authorities for marketing authorisation (reduced financial burden) • Possible use to derive Environmental Quality Standards • Issue currently discussed in the framework of the revision of the veterinary medicinal products legislation • Enhanced adaptability to scientific and technical progress as it is easier to regularly update fate and effect studies collated in substance dossiers than in individual product submissions 	<p>Threats</p> <ul style="list-style-type: none"> • Setting up the procedure would incur additional costs at first (even if in the long run the financial burden would be reduced) • Resources and time for the revision/update of the relevant pieces of legislation/guidelines, which can be a lengthy and potentially resource-intensive procedure
Further information	
<ul style="list-style-type: none"> • The German Federal Environment Agency (UBA) has initiated a project to investigate how to implement such a substance-based approach in EU legislation, with an assessment of the impact of the establishment of such a system on involved stakeholders. • REACH uses such a data sharing approach for the registration of industrial chemicals 	
Selected references	
<p>Stakeholder consultation</p> <p>Rönnefahrt,I. (2014). <i>Monograph system of active pharmaceutical substances: necessity, challenges and perspectives</i>, at the Workshop "Monograph system on active pharmaceutical substances", Brussels, 26 November 2014</p> <p>Rönnefahrt,I. (2014). <i>The monograph system: What is included and how could it be organised? – Poster</i> from the workshop "Monograph system for active pharmaceutical substances", Brussels, November 2014</p>	

Objective	Ensuring the scientific robustness, consistency and transparency of risk assessments		
Option 7: Ensure that ERA results are systematically considered in the overall benefit/risk analysis for the authorisation of human pharmaceuticals			
Context			
<ul style="list-style-type: none"> • Access to pharmaceuticals is essential to public health. The mechanics of bringing a medicine to the market are an important factor in determining access, and the EU is committed to encouraging innovation and making access to medicines easier with the scope of existing laws and regulations. For instance, the Commission appointed in 2015 an expert group on safe and timely access to medicines for patients (known as STAMP), which provides advice and expertise to the Commission services in relation to the implementation of the EU pharmaceuticals legislation, as well as programmes and policies in this field. • While access to pharmaceuticals is a priority, it is also important that the environmental impacts of those pharmaceuticals be as low as possible. According to the VMP legislation, ERAs must be taken into account in the overall benefit/risk analysis which influences the delivery of a marketing authorisation (MA). This is not the case for HMPs. In both cases (VMPs and HMPs), however, ERA can influence risk management measures when environmental risks cannot be excluded at the end of the procedure (Phase II, Tier B) (see Option 15). • Yet, ERA results are not decisive in the MA process for HMPs, and there is a lack of clarity regarding generic medicines. 			
Description			
<p>This option aims to ensure that ERA outcomes are systematically considered in the overall benefit/risk analysis. Potential risks to the environment would therefore be taken into account in the decision to grant a MA for a HMP or not, in light of the relevance of therapeutic benefits and the availability of alternatives, or in the implementation of risk mitigation measures. This could be implemented by amending the EU legislation on HMPs in the light of existing provisions for VMPs and ensuring relevant environmental expertise on scientific committees involved in the evaluation of MA applications (see Option 4).</p>			
Preliminary assessment			
Strengths <ul style="list-style-type: none"> • Prevent the marketing of substances posing significant risks to the environment, provided therapeutically effective suitable alternatives are already available. • Trigger discussion on effective alternatives to environmentally harmful active substances • Improved quality of ERAs. 	Weaknesses <ul style="list-style-type: none"> • Require data management resources to compare authorisation dossiers with therapeutic alternatives 		
Opportunities <ul style="list-style-type: none"> • Efforts focused before the release of environmentally-harmful pharmaceuticals on the market, leading to reduced need for downstream solutions to mitigate pollution and potential indirect impact on human health. • Capitalisation on good practices and lessons-learned from current implementation in the veterinary sector and of the Biocidal Products and Plant Protection Products Regulations 	Threats <ul style="list-style-type: none"> • Need for legislative change • Possibility of disproportionate costs for the industry with regard to their R&D investments • The environmental impact should be weighed against the expected clinical benefits, from a medical and social perspective, considering also the availability and characteristics of any alternatives, in order to ensure that therapeutic needs are prioritised. 		

Further information

As an example of policy consideration, this option was proposed in the Swedish Bill of Chemicals in 2013. The Bill describes the issues the Government intends to address in this area in the period up to 2020. The test requirements for medicines should, for example, be tightened and the ERA made in connection with an application for MA of medicines should be improved. To enable environmental considerations to be taken into account in the authorisation of medicinal products, the Government, like many referral bodies, considers there to be a need for an amendment to the Directive on medicinal products for human use (2001/83/EC) so that environmental risks in use can be factored into the risk/benefit assessment according to clear criteria.

Selected references

Stakeholder consultation

Ågerstrand, M. et al. (2015). *Improving environmental risk assessment of human pharmaceuticals*. Environmental science & technology, 49(9), pp. 5336-5345.

Swedish Government. Bill number: 2013/14:39.

Government Offices of Sweden (2014). *National Pharmaceutical Strategy – Action Plan 2014*.

<http://www.government.se/contentassets/57e68c08f2f04e0490fb5638aac230f1/national-pharmaceutical-strategy---action-plan-2014>

Objective	Ensuring the scientific robustness, consistency and transparency of risk assessments
Option 8: Ensure that ERAs adequately consider Persistent Bio-accumulative and Toxic substances (PBT) and endocrine properties for the APIs, as well as the toxicity and other properties of major metabolites, degradation products and excipients: a) for human pharmaceuticals; b) for veterinary pharmaceuticals	
Context	
<p><u>PBT²² screening in the current CVMP guidelines</u></p> <p>A PBT/vPvB²³ screening is required for pharmaceuticals for human use (Human Medicinal Products or HMPs) in the first phase of the ERA.</p> <p>This is not the case for veterinary pharmaceuticals (Veterinary Medicinal Products or VMPs), for which PBT assessments as specified in the current CVMP guideline are only performed for substances entering Phase II, i.e. only for substances with a Predicted Environmental Concentrations (PEC) and Octanol-water partition coefficient above the relevant thresholds. However, for PBT substances a safe concentration in the environment cannot be established with sufficient reliability. Indeed, high but unpredictable levels may be reached in animals at the top of the food chain or in the environment over extended time periods. Therefore, consideration needs to be given to whether or not a PBT assessment should be required for (any) substances that would normally stop in Phase I of the ERA.</p> <p><u>Assessment of endocrine disruption properties in the current guidelines (CVMP and CHMP)</u></p> <p>The endocrine-disrupting effect of some pharmaceuticals which are released to the environment is subject of increasing concern in the EU. Although this aspect is generally addressed in the authorisation procedure, a specific and systematic assessment of endocrine effects would be beneficial.</p> <p><u>Screening / assessment of metabolites, degradation products and pharmaceutically active excipients</u></p> <p>Although relevant metabolites of pharmaceuticals undergoing a Phase II assessment must be taken into account, no specific recommendations have been formulated in the relevant CHMP and CVMP Guidelines. Degradation products and excipients are not considered.</p>	
Description	
<p>The level of ambition regarding the inclusion of each the elements (a. to e.) in the guidelines depends on the current work progress on these issues at EU level:</p> <p><u>a. PBT screening in Phase I of the ERA for VMPs and identification of relevant RMM for HMPs and VMPs</u></p> <p>Under the option, a PBT screening would be performed during Phase I of the ERAs for VMPs. The screening procedure would be similar as the one performed for HMPs. Clear thresholds would be defined. A number of options for managing these substances have already been proposed for VMPs²⁴.</p> <p><u>b. Assessment of endocrine disruption properties for both VMPs and HMPs</u></p> <p>The European Commission proposed in July 2016 criteria to identify endocrine disruptors in the pesticides and biocides areas. Similarly, relevant criteria for pharmaceuticals with endocrine properties could be included in these guidelines.</p> <p><u>c. Phase I Screening of major metabolites and guidance for assessment in Phase II for VMPs and HMPs</u></p> <p>The guidelines would include additional details on metabolites with clear recommendations on when and how to assess metabolites in ERAs. In particular, prioritisation methods will have to be outlined, based on the toxicity and/or the expected environmental concentration of those</p>	

²² Persistent, Bio-accumulative, Toxic substances

²³ very Persistent, very Bio-accumulative substances

²⁴ AEHG, 2016

metabolites.

d. Assessment of potential risks from degradation products for VMPs and HMPs

Under the option, the guidelines would include provisions to identify and assess degradation products in Phase II of the ERA (for both HMPs and VMPs). Values of Koc and LogD at environmentally-relevant pH could be used as thresholds for such an assessment

e. Need and approach to perform an ERA for some excipients for VMPs and HMPs

Exploratory work would be performed for this element, inter alia: criteria for identifying excipients, the strategy for assessing them (screening and/or full assessment), etc.

Preliminary assessment

Strengths

- Consistent PBT assessment of human and VMPs
- **Resources and expertise:** An ad-hoc Expert Group (AHEG) (with representatives from the CVMP, the CVMP Environmental Risk Assessment Working Party (ERAWP) and EU MS) was set up to develop a strategic approach to the assessment of the risks posed by veterinary medicinal products containing (potential) PBT substances and could contribute to the implementation of this option.

Weaknesses

- **Knowledge gaps:** Little work has been done on methodologies to include and prioritise metabolites, degradation products, endocrine disruptors or excipients (e.g. how to determine eligible substances)

Opportunities

- Option **consistent with the approach for HMPs**, with themes included in the **upcoming work program of the CHMP for the revision of ERA guidelines**²⁵
- Issues currently discussed in **the framework of the revision of the veterinary medicinal products legislation**

Threats

- **Time-to-market:** More stringent ERAs may delay access of pharmaceuticals to the market while they could meet a therapeutic need

Further information

General:

The CHMP recently highlighted in its concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/4447/00 corr 2) the need to review:

- The tiered approach strategy and triggers for further assessment and additional studies;
- Whether the approaches for substances with specific properties (e.g. PBT substances, endocrine disruptors, mixtures, substances highly toxic to specific taxonomic groups) are still adequate (CHMP, 2016).

Focus on PBT properties:

The work of the AHEG regarding a strategic approach to the assessment of the risks posed by veterinary medicinal products containing (potential) PBT substances provides concrete elements to revise the approach towards PBT (CVMP, 2016). The AHEG met on seven occasions between April and December 2015 and agreed on the following points (inter alia):

- There is a need to determine the PBT status of substances used in VMPs (both new substances and existing substances)
 - For new substances, an assessment of PBT status should be conducted prior to, or at the time of, the initial application for marketing authorisation;
 - For existing substances, an initial screening for substances of concern (potential PBT

²⁵ CHMP, 2016

substances) is required.

- Consideration needs to be given to whether or not a PBT assessment should be required for (any) substances that would normally stop in Phase I of the ERAs;
- Any consideration of PBT status by CVMP needs to be in line with the approach to PBTs taken under other frameworks. There needs to be a coordinated/harmonised approach to PBT classification across all legislative frameworks;
- Where products containing PBT substances are authorised/maintained, it should be considered if the marketing authorisation should be subject to conditions, e.g. a Risk Management Plan (RMP), specific monitoring and specific pharmacovigilance requirements.

Focus on endocrine disruptors:

Commission presented on 15 June 2016 two draft legal acts – one under the Biocidal Products legislation, the other under the Plant Protection Products legislation– which set the criteria to identify endocrine disruptors.

Selected references

Legal ground

CVMP/VICH, 2000. Guideline on Environmental impact assessment (EIAs) for veterinary medicinal 565 products (VMPs) – Phase I, VICH GL 6 (CVMP/VICH/592/1998)

CVMP/VICH, 2005. Guideline on Environmental impact assessment for veterinary medicinal products - Phase II, VICH GL 38 (CVMP/VICH/790/03-FINAL)

CHMP (2006) Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 2)

Other sources

Stakeholder consultation

Ågerstrand, M. et al. (2015). *Improving environmental risk assessment of human pharmaceuticals*. Environmental science & technology, 49(9), pp. 5336-5345.

AHEG (2016). *Work of the AHEG regarding a strategic approach to the assessment of the risks posed by veterinary medicinal products containing (potential) PBT substances:*

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500202512.pdf

CHMP (2016); CHMP (2016). *Concept paper on the revision of the 'Guideline on the 4 environmental risk assessment of medicinal products for 5 human use' (EMA/CHMP/SWP/4447/00 corr 2)*

CVMP (2016). *Reflection paper on the authorisation of veterinary medicinal products containing (potential) persistent, bio-accumulative and toxic (PBT) or very persistent and very bio-accumulative (vPvB) substances* (EMA/CVMP/448211/2015), February 2016

Küster, A., & Adler, N. (2014). *Pharmaceuticals in the environment: scientific evidence of risks and its regulation*. Philosophical Transactions of the Royal Society of London B: Biological Sciences, 369(1656).

Objective	Promoting "greener" manufacturing processes		
Option 9: Under the Industrial Emissions Directive, review and revise Best Available Techniques Reference (BREF) documents relevant to emissions from the manufacturing of pharmaceuticals			
Context			
<ul style="list-style-type: none"> Some aspects of the manufacture of an active pharmaceutical ingredient (API), as well as the manufacture of the final pharmaceutical product, either together or separately, fall within the scope of the Industrial Emissions Directive (IED). However, the IED does not set emission limit values for APIs, nor require specific management practices nor the monitoring of APIs released during the manufacturing stage. Under the IED, two Best Available Techniques (BAT) reference documents (BREF) are relevant to pharmaceuticals: <ul style="list-style-type: none"> The 2006 BREF for Organic Fine Chemicals (OFC); The 2016 BREF related to the Common Waste Water and Waste Gas Treatment/ Management Systems in the Chemical Sector (CWW). The IED has made BAT conclusions mandatory in the permitting process (Article 14(3) of the IED). However, the BREFs only focus on standard parameters which are not always of direct relevance to the environmental challenges of pharmaceutical production, and do not include emission limits for APIs amongst the few micro-pollutants targeted. 			
Description			
<p>This option proposes to review, and possibly revise, relevant BREFs, such as the BREF OFC and the BREF CWW, in order to better take into account environmental concerns related to the manufacturing of pharmaceutical products, e.g. through:</p> <ul style="list-style-type: none"> The definition of standards for emissions of priority active pharmaceutical ingredients (APIs) in wastewater; The update of practices in the light of the recent developments in "green" chemistry; The systematic monitoring of relevant pharmaceutically active substances, including APIs, and transformation products and/or relevant excipients in manufacturing effluents. 			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> Use of an existing binding legal instrument focused on the environment Success stories from industry front-runners 		<ul style="list-style-type: none"> Limited to the manufacturing of pharmaceuticals within the EU, while a large share of manufacturing takes place outside of the EU 	
Opportunities		Threats	
<ul style="list-style-type: none"> Relevant timing for BREF OFC revision, not revised since its creation in 2006 Level playing field in the EU, through the specification of best practices, emission limits or monitoring requirements. Systematic monitoring of emissions as a first step before setting appropriate emission limits Direct relevance to the Water Framework Directive and other environmental legislation 		<ul style="list-style-type: none"> EU manufacturers may be at a disadvantage compared to companies relying on pharmaceutical imports It could be some time before the most relevant BREF (for OFC) is reviewed There may be technical challenges involved in including BAT specifically for pharmaceutical production, especially because few data currently exist on manufacturing emissions in the EU 	

Further information

Several examples from the industry seem to indicate that greener practices are being progressively introduced, voluntarily, at the development and manufacturing stage, within pharmaceutical companies' own operations. They could provide relevant material to define Best Available Techniques in the field of pharmaceuticals manufacture.

- As part of the *Innovative Medicines Initiative (IMI)* (a partnership between the European Union and the European pharmaceutical industry), represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the FP7 project CHEM21 (26.4 Mio EUR), funded from 2012 to 2016, focused on Green Chemistry. Entitled Chemical manufacturing methods for the 21st century pharmaceutical industries, this project aims to generate a range of methods to make the drug development process more environmentally-friendly, which will ultimately help cut costs and provide access to cheaper medicines to patients.
- Created in 2005, the *ACS GCI Pharmaceutical Roundtable* (including e.g. AstraZeneca, F. Hoffman-La Roche Ltd., Johnson & Johnson, Novartis, Pfizer Inc., Sanofi) aims to encourage innovation while catalysing the integration of green chemistry and green engineering in the pharmaceutical industry.
- As an example of improved process, Janssen reports that Abiraterone acetate, the active ingredient in ZYTIGA™, a treatment for prostate cancer, was manufactured with two rather than eight solvents, utilising 64% less raw material and 78% less water. Similarly, for Buprenorphine, hazardous waste was reduced by 28%, in addition to 42% reduction of process mass intensity, 64% raw material reduction during cleaning, 71% reduction in water consumption and 85% reduction in energy consumption.

Selected references

Legal ground

Legislative documents IED, 2010/75/EU

2006 Reference Document on Best Available Techniques for the Manufacture of Organic Fine Chemicals: http://eippcb.jrc.ec.europa.eu/reference/BREF/ofc_bref_0806.pdf

COMMISSION IMPLEMENTING DECISION (EU) 2016/902 of 30 May 2016 establishing best available techniques (BAT) conclusions, under Directive 2010/75/EU of the European Parliament and of the Council, for common waste water and waste gas treatment/ management systems in the chemical sector: http://eippcb.jrc.ec.europa.eu/reference/BREF/BATC_CWW.pdf

Other sources

Stakeholder consultation

ACS Chemistry for Life website: <https://www.acs.org/content/acs/en/greenchemistry/industry-business/pharmaceutical.html>

CHEM21 project website: <https://www.imi.europa.eu/content/chem21>

Janssen webpage on green initiatives: <http://www.janssen-verslag-samenleving-2013.be/en/ecological-sustainability/groene-initiatieven/overzicht.htm>

Lakemedelsverket, (2011). *Swedish National Pharmaceutical Strategy 2011*.

Lakemedelsverket, (2016). *Swedish National Pharmaceutical Strategy 2016 – 2018*, <https://lakemedelsverket.se/upload/om-lakemedelsverket/NLS/The%20National%20Pharmaceutical%20Strategy%202016-2018.pdf>

Objective	Promoting "greener" manufacturing processes		
Option 10: Prepare a sectoral reference document under the European Eco-Management and Audit Scheme (EMAS) to promote increased adoption by pharmaceutical companies, and by their global suppliers, of good environmental manufacturing standards			
Context			
<ul style="list-style-type: none"> • EMAS is a management instrument developed by the European Commission for companies and other organisations to evaluate, report, and improve their environmental performance. This performance extends to their supply chain, beyond EU borders. • Within EMAS, sectoral reference documents specify techniques, measures or actions that are most advanced in terms of environmental performance (energy efficiency, resource efficiency, emissions, but also supply chain management) and which are already implemented by forerunners organisations within the sector. • Thus far, these documents only concern the following sectors: retail trade, tourism, construction, public administration, agriculture, food and beverage manufacturing. 			
Description			
This option aims to develop a sectoral reference document in the EU Eco-Management and Audit Scheme (EMAS) for the pharmaceutical sector, in order for manufacturers and import companies to voluntarily implement better environmental manufacturing practices and extend their environmental responsibility to their supply chain.			
Preliminary assessment			
Strengths <ul style="list-style-type: none"> • Applicable worldwide, thus especially helpful as outsourcing increases: responsibility of manufacturers / importers beyond the EU • Recognised by the industry: since the instrument encourages better environmental practices while promoting competitiveness • Credibility and transparency: due to the external and independent nature of the EMAS registration process • Originally tailored to manufacturing companies • Relatively short timescale: 2-3 years from a company's decision to participate in EMAS until the first registration 	Weaknesses <ul style="list-style-type: none"> • Heterogeneous implementation of EMAS in the EU MS: since EMAS remains a voluntary instrument 		
Opportunities <ul style="list-style-type: none"> • Visibility and emulation: opportunity for companies to be part of a network of front runners in the field of environment and share their experience • Successful examples from the industry could encourage further participation 	Threats <ul style="list-style-type: none"> • Coherence with EMAS agenda for revision: no sectoral reference document currently planned, and other work underway, so there may be delays • Administrative burden, i.e. possible costs of EMAS implementation: average of €48,000 per company for the first year and € 26,000 annually for subsequent years²⁶ • Low existing participation of the pharmaceutical industry in EMAS • Potential lack of support from registered organisations 		

²⁶Milieu & RPA, 2009

Further information

As a forerunner, Sweden provides an example of public initiative targeting the possible impacts from the manufacturing stage. The 2011 Swedish National Pharmaceutical Strategy (NPS) encouraged **voluntary improvements in the manufacturing of pharmaceuticals through the introduction of a voluntary environmental assessment**. It has since then been revised to become the Swedish national Pharmaceutical Strategy 2016-2018, which reinforces the need to address environmental concerns in the production and use of medicines.

As highlighted in [Option 3](#), **several examples from the industry show that "greener" practices are being progressively introduced, voluntarily, at the development and manufacturing stage**, within pharmaceutical companies' own operations. **Pharmaceutical companies are also increasingly tackling the issue of their supply chain**, individually (e.g. the Johnson & Johnson (J&J) Standards for Responsible External Manufacturing prescribe minimum requirements for environmental protection) or as part of joint initiatives, such as the *Pharmaceutical Supply Chain Initiative (PSCI)*, through the voluntary definition of minimum requirements for their suppliers.

The *PSCI* (a non-profit business membership organisation formed in 2006 and legally established in the United States) is an international group of pharmaceutical companies that joined forces to promote responsible supply chain management and committed to more sustainability in pharmaceutical production. On 15 June 2016, PSCI ran a second webinar in a series designed to support manufacturing sites on how to manage the release of APIs in wastewater. The webinar is designed for suppliers that handle APIs including API manufacturers, Contract Manufacturing Organisations, Contract research organisations, and finished goods suppliers. The PSCI proposes that its members perform audits of their suppliers, including on environmental requirements.

Selected references

Stakeholder consultation

EEA website on EMAS registrants: <http://www.eea.europa.eu/data-and-maps/indicators/number-of-organisations-with-registered/assessment>

EMA Report and statistics: <http://ec.europa.eu/environment/emas/register/reports/reports.do> [consulted on 06/06/2016]

EMAS website: <http://ec.europa.eu/environment/emas/> [consulted on 06/06/2016]

J&J Standards for Responsible External Manufacturing prescribe minimum requirements for environmental protection: <https://www.jnj.com/sites/default/files/pdf/standards-for-responsible-external-manufacturing.pdf>

JRC SUSPROC website: <http://susproc.jrc.ec.europa.eu/activities/emas/>

Milieu & RPA (2009) *Study on the Costs and Benefits of EMAS to Registered Organisations*. Study Contract No. 07.0307/2008/517800/ETU/G.2. October, 2009

Pharmaceutical supply chain initiative website: <https://pscinitiative.org/home>

Objective		Promoting "greener" manufacturing processes	
Option 11: Ensure that EU Good Manufacturing Practices (GMP) address discharges of active pharmaceutical ingredients (APIs), degradation products and excipients into the environment			
Context			
<ul style="list-style-type: none"> • EU principles and guidelines of good manufacturing practices (GMP) for medicinal products for human use (HMPs) and veterinary use (VMPs) and their excipients are laid down respectively in Directive 2003/94/EC and Commission Directive 91/412/EEC further specified in EudraLex Volume 4. • The holder of a manufacturing or import authorisation must comply with these requirements and prove that the plant where the API or finished product was manufactured is subject to control and enforcement of EU-equivalent GMP. • These guidelines focus on ensuring the quality and safety of the manufacturing stage. They do not include any reference to potential impacts on or risks to the environment. 			
Description			
<p>This proposal is likely to require amending the GMP legislation in order to:</p> <ul style="list-style-type: none"> • Ensure that aspects of environmental protection fall within the scope of GMP, e.g. through setting specific environmental requirements for manufacturers of medicinal products, such as monitoring and limiting discharges and emissions of APIs into the water environment, or more stringent requirements for cleaning techniques at production facilities); • Introduce an environmental certification that could apply to pharmaceutical production facilities and that would consider environmental emissions of APIs. This environmental certification could rely on existing regulatory environmental standards or introduce voluntary programmes, e.g. on Green Chemistry, with more stringent standards; <p>To complement the above, GMP could be made a basic requirement in procurement policies.</p> <p>This option could be viewed as a complementary option to enhanced rules on waste and emission controls.</p>			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> • Success stories: Green Chemistry for more than a decade by industry front-runners 		<ul style="list-style-type: none"> • GMP focus is on health and safety and relies on scientific and engineering expertise related to health and safety, not ecotoxicological and environmental expertise 	
Opportunities		Threats	
<ul style="list-style-type: none"> • Creation of level playing field with manufacturers in the EU and outside the EU through environmental requirements for all companies concerned • Natural synergies: between actions to improve quality and safety in manufacturing and those to reduce environmental impacts • Proactivity: such an option would be an opportunity for the EU to take a position on this issue, proactively, and drive the revision of international GMP guidelines and legislation 		<ul style="list-style-type: none"> • Technical challenges: GMP should be integrated early in the drug discovery and development process, as changes in the way drugs are manufactured are difficult once the substance has been approved by regulatory authorities²⁷ • Administrative burden: need for control mechanisms, revision of Mutual Recognition Agreements (e.g. with Australia, Israel, Switzerland, Brazil, Japan, United States), and for submission of any additional requirements to the WHO, where GMP guidelines are 	

²⁷ Manley, 2015

discussed

- **Slow economic and environmental paybacks** of changes in processes due to regulatory approval time²⁸
- **Competitive disadvantage:** possible cost disadvantage when exporting pharmaceuticals
- **Access to pharmaceuticals:** risks to pharmaceuticals supply if suppliers do not comply with the legislation

Further information

Several examples from the industry show that "greener" practices are being progressively introduced, voluntarily, at the development and manufacturing stage, within pharmaceutical companies' own operations and in their supply chain. They could provide relevant material to define environmental GMP in the field of pharmaceuticals.

Selected references

Legal ground

Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines. Available at: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm [07/06/2016]

New rules on importing active pharmaceutical ingredients into the European Union - Health and Consumers (http://ec.europa.eu/health/human-use/quality/index_en.htm) [07/06/2016]

Other sources

Stakeholder consultation

Dunn, P. J. (2013). *Pharmaceutical Green Chemistry process changes – how long does it take to obtain regulatory approval?* Green Chemistry, Issue 11, 3099-3104.

European Commission - DG Health and Food Safety. (2016, 06 07). *Quality of medicines and Good Manufacturing Practices (GMP)*. Retrieved from Medicinal products for human use: http://ec.europa.eu/health/human-use/quality/index_en.htm

Manley, J. B. (2015). *The Five Ws of Pharmaceutical Green Chemistry*. In *Green Chemistry Strategies for Drug Discovery*. RSC Drug Discovery.

²⁸ Dunn, 2013

Objective	Ensuring environmental risks are adequately taken into account and translated into mitigation actions	
Option 12: Instigate an Environmental Risk Assessment (ERA) catching-up procedure for relevant pharmaceuticals for which there is still no or only an incomplete ERA		
Context		
<p>ERA results are missing for the majority of the 3,000 APIs currently on the EU market:</p> <ul style="list-style-type: none"> • HMPs: <ul style="list-style-type: none"> - Although an “<i>indication of any potential risks presented by the medicinal product for the environment</i>” is required since January 1995, when Directive 93/39/EEC entered into force, the requirement for an evaluation of potential environmental risks (i.e. ERAs) was introduced only by Directive 2004/27/EC, which came into force on 30 October 2005. Therefore, HMPs which entered the EU market before this date do not include an ERA. This is <i>inter alia</i> the case for pharmaceuticals still widely consumed (Paracetamol, Levothyroxin, etc.). Furthermore, until December 2006, no guideline on the ERA for HMPs has been in force, therefore no assessments have been done in most EU MS; - Generics may be authorised without an ERA if the applicant is able to prove that no increase of environmental exposure to the pharmaceutical substance is expected (waiving of this obligation is frequent in practice). The requirement for an ERA for a generic product does not depend on the availability of ERA results for the reference product. • VMPs: <ul style="list-style-type: none"> - The requirement to perform an ERA dates back to 1998 (when the first ERA guideline entered into force), so VMPs which reached the EU market before that date did not have to undergo an ERA; - Since 2004, submission of an ERA is required for generics. The Phase II testing guideline came into effect in 2005. - Since 2005, the ERA guidelines are in place; assessments performed before that date may need to be updated. 		
Description		
<ul style="list-style-type: none"> • This option proposes to require ERAs from Marketing authorisation holders for “old” VMPs and HMPs (i.e. pharmaceuticals already on the market) which are still on the market and are the most likely to pose environmental risks or which have posed environmental risks in the past. • This “catching-up” procedure could be based on the model that applies to other regulated chemical substances (REACH, plant protection products, biocides) and would focus on APIs. • Pharmaceuticals would be prioritised for review based on information about their risks to the environment. For many APIs, this would mean a review before the need for renewal of their authorisation. (If ERAs were to be revised at the time of authorisation renewal only, not many pharmaceuticals would be covered in practice. For instance, in Germany, only one human pharmaceutical authorization was renewed in the past five years.) 		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Representative picture of environmental risks for all priority pharmaceuticals • Information likely to be more easily available for the assessment (hazard and environmental exposure, chronic effects and long-term impacts) since it concerns molecules which have been used for a long time (e.g. Paracetamol, Levothyroxin). • Similar level of assessment for all 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Requires discussing how to allocate responsibilities for generic products • Products with the same active substance would still need separate ERAs (requiring duplicated studies on fate, effects etc.) unless a system to share data were put in place (see option 6) 	

pharmaceuticals on the market	
<p>Opportunities</p> <ul style="list-style-type: none"> • Proportionality if prioritise pharmaceuticals with incomplete ERAs for assessment based on estimated risk • Additional costs can be shared by marketing authorisation holders if the active substance is used in many products and can be limited for agencies which will benefit from not conducting multiple assessment • Lessons learnt from other pieces of legislation such as REACH, Biocides and the Plant Protection Products regulation, which cover all substances regardless of the date they were put in the market. • Issue currently discussed in the framework of the revision of the veterinary medicinal products legislation 	<p>Threats</p> <ul style="list-style-type: none"> • Time-consuming process since the majority of the 3,000 APIs currently used in the EU market were authorised before 2005 • Increased costs for marketing authorisation holders that have to perform the ERA (unless they agree to share costs) • Administrative costs for EMA, national medicines agencies and other regulators
Further information	
<ul style="list-style-type: none"> • Before REACH – i.e. before 2007 – the EU chemicals legislation had separate regimes for existing (“old”) substances and new substances. With REACH, all industrial chemicals are considered, regardless of the date on which they were put in the market²⁹. The different steps towards a common procedure could provide a good example for the field of pharmaceuticals. • The initiative Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE) (2015 – 2018, http://i-pie.org/) aims to establish a framework that uses information from toxicological studies, pharmacological mode of action and in silico models to support intelligence-based environmental testing of pharmaceuticals in development and to prioritise legacy pharmaceuticals (prior to 2006) (ECT, 2015). 	
Selected references	
<p>Stakeholder consultation</p> <p>Ågerstrand, M. et al. (2015). <i>Improving environmental risk assessment of human pharmaceuticals</i>. Environmental science & technology, 49(9) pp. 5336-5345.</p> <p>ECT (2015). <i>Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE)</i>. http://i-pie.org/</p> <p>Touraud, E., Roig, B., Sumpter, JP., Coetsier, C. (2011). <i>Drug residues and endocrine disruptors in drinking water: Risk for humans?</i> International Journal of Hygiene and Environmental Health, 214: 437-41</p>	

²⁹ There are a few exceptions (e.g. polymers) but they do not relate to the date of market entry.

Objective	Ensuring environmental risks are adequately taken into account and translated into mitigation actions
Option 13: Require from the marketing authorisation holder the update/revision of ERAs based on post-marketing monitoring data or newly published information	
Context	
<ul style="list-style-type: none"> • When ERAs are performed, there are often information gaps concerning environmental concentrations of the API from the product of interest (since the product is not yet commercialised, unless it is a generic). • Currently, Marketing Authorisation Holders (MAHs) are required to revise their ERAs if a significant increase in the environmental exposure is expected, as a result of an extension (e.g. new indication or inclusion of new forms of administration) or of a Type II variation³⁰. A stand-alone ERA can also be submitted 'in exceptional circumstances' as a Type IB Variation³¹, however there is no guidance as to what would trigger such action. • Except for those cases, the availability of new data can only impact future marketing authorisations (MAs), that is, new products containing the same API. • This is problematic since new knowledge may emerge at any time once the product is commercialised and used on a large scale; and new information may sometimes necessitate revision of the risk assessment conclusions. 	
Description	
<ul style="list-style-type: none"> • This option aims at requiring ERAs to be updated whenever new information becomes available that is important for the evaluation of the environmental risks posed by the product concerned. • This information could include evidence of a significant exposure and/or impact of the relevant API on the environment, such as: <ul style="list-style-type: none"> - Availability of new Measured Environmental Concentrations (MECs), higher than the Predicted Environmental Concentrations (PECs) considered for the original MA application; - Evidence from environmental monitoring that one or more environmental compartments are adversely affected by the API; - Administrative triggers, such as patent expiry; MA for similar active substances (likely to have an impact through cumulative PECs); - New research results on the effects or fate of the API, e.g. from studies with relevant non-standard organisms. • Guidelines would specify to assessors and MAHs the categories of new information that should trigger update of an ERA, as well as recommendations on relevant data-gathering approaches and information sources (post-market monitoring methods, databases, relevant organisations, etc.), and a list of the information to be reported by the MAH, possibly including environmental monitoring data gathered by the MAH itself. • Guidelines would include procedures for assessors and MAHs to follow if the update leads to a change in the conclusions of the ERA, including information on generic risk management measures that might be relevant. <p>If environment agencies or expert networks were involved in post- marketing monitoring for HMPs and VMPs, they could alert relevant medicines agencies, at national or EU level.</p>	

³⁰ Change which may have a significant effect on the quality, safety or efficacy of the medicinal product concerned, unlike Type I variation which is a change that has only a minimal effect, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned. The types of change considered are listed in the Annexes to the Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of MAs for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

³¹ A minor change to a MA that the MAH must notify to the regulatory authority before implementation, but which does not require formal approval.

Preliminary assessment	
<p>Strengths</p> <ul style="list-style-type: none"> • Updated state of knowledge • Databases to help with the update: e.g. European database on suspected adverse drug reactions, monitoring data from Member States, including for substances on the Watch List under the Water Framework Directive; monitoring data obtained by MAH; research project outputs 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Pre-requisite for some aspects of this mechanism: effective post-market environmental monitoring, data gathering and communication. • Need for legislative changes
<p>Opportunities</p> <ul style="list-style-type: none"> • Increased collaboration between stakeholders. • Regulatory precedent with the requirement of Art 22 of the REACH regulation: "Following registration, a registrant shall be responsible on his own initiative for updating his registration without undue delay with relevant new information [...]" • Issue currently discussed in the framework of the revision of the veterinary medicinal products legislation 	<p>Threats</p> <ul style="list-style-type: none"> • Impacts on resources and costs for medicines agencies, possibly environment agencies, and the MAH
Further information	
<ul style="list-style-type: none"> • The pharmaceuticals industry is promoting the concept of Extended ERA, including: <ul style="list-style-type: none"> - Consideration of the Total PEC arising from all products containing the same API; - Assessing the robustness of all research findings (internal and external), following up with additional laboratory testing where necessary, and assessing the likelihood that the research finding can translate into an adverse population-level impact in the field; - If necessary, in cases where potential environmental risks are identified, looking for indicators of the effect on wildlife through targeted sampling where concentrations can be expected to be at their highest. <p>This extended ERA would be conducted in close association with post-marketing monitoring by the MAH. If the latter does not indicate any significant risk from an API, then no further action is needed unless the review of the ERA based on Total PEC (conducted for instance at the expiry of pharmaceutical patents) demonstrates reasons for concern.</p> • The requirement for updates already exists in other policy fields, with frequent updates required in the context of the REACH Regulation and the Biocides and Plant Protection Products Regulation – for biocides and plant protection products the initial approval shall not exceed 10 years, and in some cases 5 years (Article 4(1) in the biocide regulation, Article 5 in the plant protection product regulation). • The UBA in Germany recently launched its database on the global occurrence of pharmaceuticals, which provides new information on measured environmental concentrations of pharmaceutical substances: https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0. 	
Selected references	
<p>Legal ground</p> <p>CVMP/VICH (2000) Guideline on Environmental impact assessment (EIAs) for veterinary medicinal 565 products (VMPs) – Phase I, VICH GL 6 (CVMP/VICH/592/1998)</p> <p>CVMP/VICH (2005) Guideline on Environmental impact assessment for veterinary medicinal products - Phase II, VICH GL 38 (CVMP/VICH/790/03-FINAL)</p> <p>CHMP (2006) Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 2)</p> <p>Regulation (EC) No 1907/2006 of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency</p> <p>Regulation (EC) No 1107/2009 of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC</p>	

Regulation (EU) No 528/2012 of 22 May 2012 concerning the making available on the market and use of biocidal product

Other sources

Stakeholder consultation

Ågerstrand, M. et al. (2015). *Improving environmental risk assessment of human pharmaceuticals*. *Environmental science & technology*, 49(9), 5336-5345.

CHMP (2016). *Concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use'* (EMA/CHMP/SWP/65429/2016)

Objective	Ensuring environmental risks are adequately taken into account and translated into mitigation actions		
Option 14: Link the need for a prescription to supply/obtain human pharmaceuticals to the results of ERAs, and provide guidelines for the enforcement of existing provisions for veterinary pharmaceuticals			
Context			
<ul style="list-style-type: none"> • The current pharmaceuticals legislation does not give the EU competence to influence the decision of putting a specific pharmaceutical under prescription or not: this is a competence of EU MS. • Nevertheless, Article 67 of Directive 2001/82/EC requires prescriptions for veterinary pharmaceuticals (VMPs) which, <i>inter alia</i>, pose a potential risk to the environment (in practice, this applies to pharmaceuticals for food-producing animals only, since exposure to pharmaceuticals for most non-food-producing animals remains below the necessary threshold to trigger an in-depth ERA assessment). However, the Directive does not specify the level of risk that should trigger the requirement for a prescription. • There is no comparable risk-related prescription requirement for human pharmaceuticals (HMPs). 			
Description			
<ul style="list-style-type: none"> • This option tackles pharmaceuticals which have been authorised in the EU but may pose a risk to the environment nonetheless: <ul style="list-style-type: none"> - HMPs for which ERA conclusions point to a potential risk to the environment; - VMPs for which an ERA was performed and – although the risk-benefit analysis led to an authorisation – points to a potential risk to the environment. • Under this option, the EU legislation for HMPs would be amended to require from EU MS prescription-only delivery for HMPs posing environmental risk. • For both HMPs and VMPs, guidelines would be developed identifying environmental risk thresholds triggering prescription-only administration of environmentally-harmful pharmaceuticals. • This option could potentially be combined with the amendment for a catching-up procedure as proposed in Option 12. 			
Preliminary assessment			
Strengths <ul style="list-style-type: none"> • Reducing consumption of potentially environmentally harmful as well as potentially harmful for human health (in the case of antibiotics) medicines, while ensuring access for patients who specifically require the medicine • Can learn from the implementation of the existing provision in the veterinary medicinal products legislation in considering whether to extend such a provision to human pharmaceuticals. 	Weaknesses <ul style="list-style-type: none"> • Scope limited to future authorisations, renewals or pharmaceuticals subject to a catch-up ERA • Uncertain effectiveness of requiring prescriptions to reduce consumption of environmentally harmful medicinal products 		
Opportunities <ul style="list-style-type: none"> • Benefits of better monitoring and control at the consumption stage, leading to reduced need for downstream solutions to mitigate environmental pollution and impact on human health (e.g. AMR) 	Threats <ul style="list-style-type: none"> • Impact on national social security systems related to prescription and reimbursement 		

Further information

This option could benefit from the lessons learnt from an initiative from the Swedish Medical Agency:

- In Sweden, a number of non-prescription medicines will undergo environmental assessment in 2016, using an environmental assessment model that has been developed under the national pharmaceutical strategy;
- This model was developed by the Swedish Association of the Pharmaceutical Industry, together with sector stakeholders, and takes account of discharges of pharmaceutical substances in production and utilisation of natural resources. The pilot study is continuously evaluated by a working group in which all stakeholders take part;
- As part of this exercise, the Swedish Medical Agency will need to evaluate how the environmental assessment can be communicated and whether there is any willingness to pay for an environmentally assessed medicine among final consumers.

Selected references

Legal ground

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

Other sources

Stakeholder consultation

Ågerstrand, M. et al. (2015). *Improving environmental risk assessment of human pharmaceuticals*. *Environmental science & technology*, 49(9), pp. 5336-5345.

Swedish Medical Agency Lakemedelsverket (2016). *Swedish National Pharmaceutical Strategy 2016 – 2018*, <https://lakemedelsverket.se/upload/om-lakemedelsverket/NLS/The%20National%20Pharmaceutical%20Strategy%202016-2018.pdf>

Objective	Ensuring environmental risks are adequately taken into account and translated into mitigation actions		
Option 15: Require Member States to designate the authority/authorities responsible at national level for the follow-up and reporting obligations linked to implementation of risk mitigation measures			
Context			
<ul style="list-style-type: none"> • The Directives on medicinal products for human and veterinary use (2001/83/EC and 2001/82/EC) and their related guidelines provide precautionary and safety measures when an environmental risk has been identified following an Environmental Risk Assessment (ERA). These measures are called Risk Mitigation Measures (RMM). • For HMPs, these RMMs consist mainly of precautionary recommendations that would be applicable to any kind of pharmaceuticals, such as recommendations for disposal of unused medicinal products or waste materials. The only binding obligation rests upon the Marketing Authorisation Holder (MAH) who must include these recommendations in the product literature (Summary of Product Characteristics and Product Leaflet). • For VMPs, RMMs cover pharmaceutical storage, administration to animals and disposal of waste. It is difficult, however, to control their application and ensure a thorough follow-up. Furthermore, there is no clear responsibility regarding implementation due to a lack of a legal basis for the enforcement of RMMs. 			
Description			
<ul style="list-style-type: none"> • This option aims at ensuring that implementation of Risk Mitigation Measures (RMM) becomes an obligation, particularly for the manufacturer, prescribers and personnel in charge of waste collection and disposal. • An obligation should be imposed at EU level for EU MS to designate authorities in charge of controlling the setting of RMM and compliance. • Appropriate legal instruments should be established in the Directives on medicinal products for human and veterinary use (2001/83/EC and 2001/82/EC) to enforce compliance with RMM and penalise infringements. • Guidelines on Risk mitigation measures for HMPs in the environment could be developed. Guidelines have already been developed for VMPs by the ERA Working Party. 			
Preliminary assessment			
Strengths <ul style="list-style-type: none"> • Greater compliance with RMMs of all actors (manufacturer, prescribers, users) • Appropriate level of implementation and enforcement of the legislation • Improved communication of environmental risks to operators and end users 	Weaknesses <ul style="list-style-type: none"> • Clear criteria for compliance need to be defined for appointing authorities to apply • Need to harmonise reporting and compliance indicators across MS 		
Opportunities <ul style="list-style-type: none"> • Financial penalties in case of infringements could contribute to the funding of the follow-up and reporting obligations of the implementation of RMM • Indirect impacts on water and health management costs • Potential synergies with other EU legislation: <ul style="list-style-type: none"> - chemical legislation, in particular pesticides - EU Water Framework Directive, which 	Threats <ul style="list-style-type: none"> • Technical challenge of defining RMM for all sources of environmental exposure to HMPs (e.g. diffuse exposure via sewage) • Need to assess concrete economic and organisational impacts to ensure the effectiveness of RMMs' implementation in each MS • Ensuring compliance would require human and financial resources for companies and reporting bodies (national 		

<p>demands measures to prevent the deterioration of the quality of surface water bodies</p> <ul style="list-style-type: none"> - For VMPs, general consistency with the Common agricultural policy and good agricultural practices promoted in certain EU MS 	<p>and European for centralisation of reporting)</p> <ul style="list-style-type: none"> • Time required to amend and transpose EU legislation
Further information	
<p>In 2014, Liebig et al. published a catalogue of proposed risk mitigation measures (RMMs) for human and veterinary medicinal products, which may support applicants and competent authorities within the process of the authorisation for (VMPs) or the disposal for HMP. (Liebig M., 2014)</p>	
Selected references	
<p><u>Legal ground</u></p> <p>CVMP (2007). <i>Revised Guideline on Environmental Impact Assessment for Veterinary Pharmaceuticals in support of the VICH Guidelines GL6 and GL38 (VICH-TGD)</i>, adopted by CVMP on 18 April 2007, came into effect on 1 November 2007, Doc. Ref. EMEA/CVMP/ERA/418282/2005-Rev.1</p> <p>CVMP (2005). <i>Guideline on Environmental impact assessment for veterinary medicinal products - Phase II</i>, VICH GL 38 (CVMP/VICH/790/03-FINAL)</p> <p>CHMP (2006). <i>Guideline on the environmental risk assessment of medicinal products for human use</i> (EMEA/CHMP/SWP/4447/00 corr 2)</p> <p><u>Other sources</u></p> <p>Stakeholder consultation</p> <p>EMA (2012). <i>Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products</i>. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500124187.pdf</p> <p>Liebig M., F. C. (2014). <i>Risk Mitigation Measures: An Important Aspect of the Environmental Risk Assessment of Pharmaceuticals</i>.</p>	

Objective	Ensuring environmental risks and impacts observed post-marketing are identified and reported		
Option 16: Establish routine dialogue and information exchange between relevant Member State agencies and authorities to help ensure that API levels in the environment are safe for the environment and human and animal health			
Context			
<ul style="list-style-type: none"> • Today, information exchange and collaboration between health and environmental competent authorities remain very limited. • Yet, routine dialogue would help authorities better understand each other's respective needs and constraints. In particular, early communication of the conclusions of environmental risk assessment, especially for substances representing a significant risk, would be very valuable to environmental authorities, in order to tailor their efforts for monitoring and mitigating the risks that they pose. 			
Description			
This option aims to establish and implement mechanisms for timely information sharing and routine dialogue between health, veterinary and environmental competent authorities. These could involve a systematic consultation plan, regular meetings or briefings, the use of online fora, and/or the implementation of an alert system. These mechanisms could ensure a better consideration of environmental aspects at post-marketing stage.			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> • Easier and earlier access to data for competent authorities involved in decisions relating to environmental protection • Communication between health, veterinary and environmental authorities could contribute to the good functioning of the environmental aspects of pharmacovigilance • Better coherence between monitoring and mitigation efforts 		<ul style="list-style-type: none"> • Need for resources and time for the organisation of meetings / exchange of information 	
Opportunities		Threats	
<ul style="list-style-type: none"> • Exploitation of multiple channels for information exchange • Optimisation of resources for monitoring and risk mitigation • Better synergies between health, veterinary and environmental policies 		<ul style="list-style-type: none"> • Different cultures with regard to the perception of risks, and different priorities (human and animal health, environment) • Confidentiality requirements could impede efforts to share information 	
Selected references			
Stakeholder consultation			

Objective	Ensuring environmental risks and impacts observed post-marketing are identified and reported		
Option 17: Ensure that environmental issues are a) introduced into the pharmacovigilance system for human pharmaceuticals and b) strengthened for veterinary pharmaceuticals particularly in relation to AMR			
Context			
<ul style="list-style-type: none"> • <u>Environmental aspects of pharmacovigilance for veterinary products:</u> <ul style="list-style-type: none"> - These are fully integrated in the veterinary pharmacovigilance system (CVMP, 2015). Any environmental problems observed in conditions of normal use of the product must be reported by the Marketing Authorisation Holder (MAH) in the Periodic Safety Update Reports (PSURs) submitted regularly to EMA or to the national competent authority in the EU MSs (CVMP, 2008); - Articles 47 of Regulation (EC) 726/2004 and 87 of Directive 2001/82/EC refer to the responsibility for encouraging veterinarians and other health-care professionals, animal owners and breeders to report adverse events. National legislation is also in place in various EU MS requiring veterinarians to report adverse events that come to their attention. However, safety problems in general and potential environmental problems in particular are reported relatively infrequently through pharmacovigilance tools (CVMP, 2015; CVMP, 2015b). • <u>Environmental aspects of pharmacovigilance for human products:</u> environmental aspects are not included in the pharmacovigilance system. The Directive and Regulation on pharmacovigilance (Directive 2010/84/EU and Regulation (EU) No 1235/2010) only mention the general need for EU MS to monitor and evaluate the risk of environmental effects of medicinal products for human use, and for the EU to draft a report on the scale of the problem and consider relevant amendments to the pharmaceuticals legislation. 			
Description			
<p>This option aims at:</p> <ul style="list-style-type: none"> • a) For human pharmaceuticals (HMPs), amending Directive 2001/83/EC to introduce environmental requirements into the pharmacovigilance system, based on what is already in place for VMPs; • b) For veterinary pharmaceuticals (VMPs), promoting the reporting of environmental problems for their better inclusion in PSURs, as part of the overall need to improve the reporting of adverse effects of pharmaceuticals as highlighted by the CVMP (simplify reporting process; develop an adverse event reporting app; use communication tools; develop a network of practitioners in charge of this reporting; require submission of a regular literature review by the MAHs, pay particular attention to AMR, etc.). 			
Preliminary assessment			
<p>Strengths</p> <ul style="list-style-type: none"> • Stronger pharmacovigilance will provide better information base to revise the risk-benefit ratios of a marketed pharmaceutical • For HMPs: lessons learnt from the pharmacovigilance system for VMPs • For VMPs: further actions to implement existing legislative requirements 	<p>Weaknesses</p> <ul style="list-style-type: none"> • <u>C</u>ompanies and regulatory agencies may need to devote additional resources for post-marketing environmental monitoring 		
<p>Opportunities</p> <ul style="list-style-type: none"> • For VMPs: in line with recommended improvements by CVMP for the overall pharmacovigilance system • For HMPs: consistency with the veterinary legislation 	<p>Threats</p> <ul style="list-style-type: none"> • Technical challenges: signal detection in the environment and identification of cause and effect • Uncertainties in non-spontaneous reporting from the MAH and spontaneous reporting from other sources, and in the quality of 		

<ul style="list-style-type: none"> • Synergies with on-going actions to monitor pharmaceuticals under the Water Framework Directive (WFD) 	<p>reporting</p> <ul style="list-style-type: none"> • Better collaboration between the industry and other stakeholders a pre-requisite for effective implementation
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Further information

- The CVMP published guidance on how to promote and improve pharmacovigilance reporting in the EU MS in its 2015 Reflection paper on promotion of pharmacovigilance reporting (CVMP, 2015b).
- Holm et al. 2013 assessed "ecopharmacovigilance" challenges and opportunities in the light of existing pharmacovigilance systems.
- Pharmaceutical industry trade associations (AESGP, (Association of European Self-Medication Industry), EFPIA, (European Federation of Pharmaceutical Industries and Associations), and Medicines for Europe) are promoting a concept of ecopharmacostewardship, including extended ERA during the post-authorisation phase. A few pharmaceutical companies, like AstraZeneca, are proposing a framework for post-marketing monitoring of environmental risks taking into account any new information that may be available.

Selected references

Legal basis

Directives 2001/82/EC and 2001/83/EC

Other sources

Stakeholder consultation

AstraZeneca. Environmental risk assessment data. 2012. www.astrazeneca.com/Responsibility/The-environment/Pharmaceuticals-in-the-environment/era-data-2012

Holm, G. (2013). *Implementing Ecopharmacovigilance in Practice: Challenges and Potential Opportunities*. Drug Saf, 533–546.

Medhi, B. et al. (2012). *Ecopharmacovigilance: An issue urgently to be addressed*. Indian J Pharmacol, 547–549.

Silva, L.J.G et al. (2012). *Ecopharmacovigilance. The Handbook of Environmental Chemistry* (pp. 213–42). Germany: Springer-Verlag Berlin and Heidelberg GmbH & Co. KG.

Swedish Water House. (2016). *Water and pharmaceuticals – a shared responsibility - WORKING PAPER*

Velo, G. (2010). *Ecopharmacovigilance for better health*. Drug Saf, 963–8.

CVMP (2015). *Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products:*

www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/06/WC500187803.pdf

CVMP (2008). *Recommendation on management and assessment of Periodic Safety Update Reports (PSURs) of veterinary medicinal products:*

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004981.pdf

CVMP (2015b). *Reflection paper on promotion of pharmacovigilance reporting:*

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184528.pdf

CVMP (2016). *Draft reflection paper on non-spontaneous adverse event reports (peer-reviewed literature, internet and social media)*

www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500207464&mid=WC0b01ac058009a3dc

Objective	Ensuring environmental risks and impacts observed post-marketing are identified and reported	
Option 18: Include pharmaceuticals as relevant in the watch lists for monitoring surface and groundwater under the Water Framework Directive (WFD) a) along with AMR in relevant microorganisms when antimicrobials are included; b) without requiring monitoring of AMR		
Context		
<ul style="list-style-type: none"> • The Water Framework Directive (WFD) and its daughter Directives on Groundwater and Environmental Quality Standards require an integrated approach to the monitoring and assessment of the quality of surface and ground water bodies. • <u>For surface water:</u> <ul style="list-style-type: none"> - Good chemical status depends on compliance with concentration limits set for a number of priority substances and other pollutants³². Other substances of possible concern can be added in the watch list. These substances are not subject to concentration limits in the environment but simply to EU-wide monitoring, in order to support future reviews of the priority substances list; - Currently, six pharmaceuticals (the hormonal preparations 17alpha-ethinylestradiol and 17beta-estradiol, the painkiller Diclofenac and three macrolide antibiotics) are included in the watch list. None is included in the priority list. • <u>For groundwater:</u> <ul style="list-style-type: none"> - Good chemical status depends on compliance with Groundwater quality standards for a minimum list of pollutants³³. A voluntary watch list consolidates chemicals for complementary monitoring; - Currently, no HMPs or VMPs are included in the list of standards, but pharmaceuticals have been the subject of a pilot study for the watch list³⁴. 		
Description		
<p>This option aims to include additional pharmaceuticals of relevance:</p> <ul style="list-style-type: none"> • In the watch list for surface water under the EQSD; and • In the voluntary watch list for groundwater, under the Groundwater Directive. <p>Surface water EQS and Groundwater standards should then be set for the pharmaceuticals identified as posing a risk (meaning for example that such substances are moved from the watch list to the priority list for surface water) during revision of those Directives.</p> <p>In case a), monitoring of AMR in relevant microorganisms should also be included when antimicrobials are included, to contribute to understanding the role of the environment in the emergence and spread of AMR.</p> <p>In case b), monitoring requirements would remain the same.</p> <p>Expansion of this option to cover also the monitoring of AMR in relevant microorganisms in soil could be envisaged.</p>		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Achieves better knowledge of the occurrence (MEC) and trends of pharmaceuticals and AMR in aquatic compartments to inform the review of the priority substances list and the list of groundwater contaminants • Provides means to check validity of PEC³⁵ used for 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Exercise limited to measuring concentrations in the aquatic environment, not actually regulating emissions 	

³² as listed in Annex I to the Environmental Quality Standards Directive

³³ set respectively in Annexes I and II of the Groundwater Directive

³⁴ Marsland & Roy 2016

<p>ERA and to compare MEC with PNEC³⁶ to refine ERA</p> <ul style="list-style-type: none"> • Can build on existing research work and national monitoring programmes 	
<p>Opportunities</p> <ul style="list-style-type: none"> • Priority setting for policy actions on pharmaceuticals • Can piggy-back on 2016-2018 CIS mandate to the Groundwater Working Group to develop a procedure to identify substances to be subject to the voluntary GW watch list • Opportunity to test and scale-up new monitoring tools to better take into account the potential impacts of mixtures • Potential synergies with the UWWTD and the IED 	<p>Threats</p> <ul style="list-style-type: none"> • Insufficient monitoring capability/resources in the EU MS. Likely to need additional research and harmonisation to be able to monitor all relevant substances and to decide what to monitor and where
<p>Further information</p>	
<p>Several tools could be used for the prioritisation of pharmaceuticals to be systematically monitored in surface and groundwater, such as:</p> <ul style="list-style-type: none"> • UBA database on the global occurrence of pharmaceuticals: https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0; • ERA results on estimated risk ratio; • Results from post-authorisation surveillance (eco-pharmacovigilance) with observed detrimental impacts on the environment and implementation of risk mitigation measures. 	
<p>Selected references</p>	
<p><u>Legal basis</u> Water Framework Directive (2000/60/EC) Groundwater Directive (2006/118/EC as amended by Commission Directive 2014/80/EU) Directive on Environmental Quality Standards (Directive 2008/105/EC as amended by Directive 2013/39/EU) (EQSD) Commission Implementing Decision (EU) 2015/495 establishing a watch list</p> <p><u>Other sources</u> Stakeholder consultation Marsland T & Roy S (Amec Foster Wheeler) (2016) Groundwater Watchlist Pharmaceuticals Pilot Study – Monitoring Data Collection and Initial Analysis https://circabc.europa.eu/d/a/workspace/SpacesStore/a1e23792-6ecd-4b34-b86c-dcb6f1c7ad1c/1600204%20Pharm%20Pilot%20Study.docx</p>	

³⁵ Predicted Environmental Concentration

³⁶ Predicted No Effect Concentration

Objective		Promoting sustainable use of pharmaceuticals	
Option 19: Encourage Member States to increase the consideration of environmental aspects during medical/veterinary education and advanced training of healthcare professionals including healthcare managers			
Context			
<ul style="list-style-type: none"> Doctors, veterinarians and pharmacists play key roles in decisions about pharmaceutical consumption. They interact with patients/animal owners and are able to: <ul style="list-style-type: none"> Supervise the patients' and animal owners' access to and level of consumption of medicines in general (through prescriptions and recommendations for OTC); Recommend some pharmaceuticals over others according to their therapeutic effects and suitability, thus influencing procurement decisions; and Inform patients/owners of the importance of taking precautions in their use and disposal. However, medical and veterinary education and advanced training of healthcare professionals rarely addresses the environmental aspects of pharmaceutical consumption. Information on the environmental profile of pharmaceuticals is considered by doctors when they decide which pharmaceutical to prescribe only in a few countries, like Sweden. 			
Description			
<ul style="list-style-type: none"> This option aims to foster responsible prescription and purchase of medicines, their use and disposal in EU MS, by providing knowledge and tools to doctors, veterinarians, pharmacists and other healthcare professionals about the potential environmental hazards and effects of medicinal products, via education and advanced career training. Collaboration between the European Commission, the European Medicines Agency, national competent authorities and stakeholders such as the Association of Medical Schools in Europe could be promoted, in order to provide guidance to: <ul style="list-style-type: none"> Include an environmental module in education programmes (medical, pharmacy and veterinary studies); Establish relevant professional training, including of healthcare managers responsible for procurement decisions. Educational and training material could include: <ul style="list-style-type: none"> Background information on the scale of the problem and good practices from prescription to disposal for more sustainable use of pharmaceuticals (including antibiotics); References/links to existing environmental classifications of medicinal products, which highlight more environmentally friendly alternatives with the same or sufficiently similar therapeutic effect; Guidelines for environmentally conscious procurement, prescription or recommended use, including caveats regarding individual needs and how to avoid discouraging the taking of medication that is needed. <p>This option complements Option 20, regarding information campaigns for the general public.</p>			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> Could have considerable influence on procurement, prescription, consumption and disposal behaviour (leading for example to avoidance of over-use, use of more environmentally-friendly alternative pharmaceuticals when available, treatment adherence, and limitation of inappropriate self-medication) Examples exist of effective training experiences, guidelines and databases already in place (e.g. in France, Sweden) Low costs compared to research and monitoring 		<ul style="list-style-type: none"> Little information exists on the environmental risks from pharmaceuticals currently on the market Some impacts are only indirect, e.g. on treatment adherence, self-medication and disposal behaviour. Online purchasing by patients not addressed 	

Opportunities

- **Significant benefits for public healthcare financing** (e.g. cost of unused prescribed pharmaceuticals in the UK estimated to be £300 million a year³⁷)
- **Would exploit existing interaction/contact** to achieve **general awareness raising** of the healthcare community and in turn of the patient/owner community
- Would be in line with the responsibility attributed to the prescribers, pharmacists and retailers in the 2015 Guidelines for the prudent use of antimicrobials in veterinary medicine

Threats

- **Paucity of greener alternatives in the short and possibly long term;** the field of green pharmacy is at its infancy
- **Cultural differences:** relationships between doctors, pharmacists and patients may vary between Member States
- **Influence of pharmaceutical industry** on procurement and prescription decision
- **Ingrained emphasis on therapeutic effectiveness** irrespective of environmental aspects

Further information

At the MS level, some organisations routinely organise communication actions to train healthcare professionals, such as **CESPharm**³⁸ in France for pharmacists. Training could further cover the environmental risks from pharmaceuticals, preferably in the light of national consumption statistics and other country-specific behaviour patterns.

Information could be widely communicated through the development and publication of guidelines, such as in Sweden with the **Wise List** created about 15 years ago based partly on the FASS information database. Updated annually, these regional guidelines for drug prescribers, produced by expert groups, recommend about 240 pharmaceutical products as first-line choices for outpatient treatment of common diseases, based on medical efficacy and safety as well as environmental aspects. Despite 87% of primary care physicians adhering to its recommendations, modifications of prescriptions have been limited because of the paucity of alternative and "greener" medicines (Lars et al 2011). No direct link could be made with environmental benefits, but this initiative has increased the overall awareness of the profession. The acceptance of the 'Wise List' in terms of trust among physicians and among the public and increased adherence may be explained by clear criteria for drug recommendations, a comprehensive communication strategy, and continuous medical education and involvement of professional networks and patients.

Selected references

Stakeholder consultation

ADEME (2013). *Médicaments : Collections Repères*. Paris.

Daughton C. (2014). *Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs*. Science of the Total Environment, 392-404.

European Commission (2015) Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04):

http://ec.europa.eu/health/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf

Health Care Without Harm (2014). *How Doctors Can Help Reduce Pharmaceutical Pollution*. Brussels.

Lars L., et al. (2011). *The 'Wise List' – A Comprehensive Concept to Select, Communicate and Achieve Adherence to Recommendations of Essential Drugs in Ambulatory Care in Stockholm*. Basic & Clinical Pharmacology & Toxicology.

Norman C., et al. (2009). *Potential savings without compromising the quality*. The International Journal of Clinical Practice, 1320–1326.

The Stockholm City Council (2015). *The Wise List 2015*:

http://www.janusinfo.se/Documents/Kloka_Listan/The-Wise-List-2015.pdf

The Swedish Association of the Pharmaceutical Industry AB. (2008). FASS The Swedish Information Search Engine.

Wennmalm A. (2010). *The potential for better communication between doctors, pharmacists and patients*. In EEA (2010), Pharmaceuticals in the environment. Technical report No 1/2010. Available at: www.eea.europa.eu/publications/pharmaceuticals-in-the-environment-result-of-an-eea-workshop

York Health Economics Consortium (2010) Evaluation of the Scale, Causes and Costs of Waste Medicines

³⁷ York Health Economics Consortium, 2010

³⁸ www.cespharm.fr/fr/Prevention-sante

Objective	Promoting sustainable use of pharmaceuticals		
Option 20: Ensure the provision of information to the general public that encourages the sustainable use of pharmaceuticals, in particular antimicrobials			
Context			
<ul style="list-style-type: none"> • Although public awareness of the need to dispose correctly of unused medicines has increased, most people are not aware that consumption itself (and subsequent excretion) is the main source of pharmaceuticals in the environment. They are not necessarily aware that their decision to ask for a prescription or to take a particular medicine could have an effect on the environment. • The increased scope for patients to self-medicate, including with products obtained online, has led to an increase in the prevalence of this practice, and possibly to additional unnecessary use. • While human health and animal well-being must remain a priority, actions to better inform the public on how to use and dispose of pharmaceuticals more sustainably could reduce environmental risks and impacts. 			
Description			
<p>This option aims to encourage EU MS to implement information campaigns on the environmental risks potentially posed by the use and disposal of pharmaceuticals and the impacts of our everyday practices in this respect, as users or handlers. EU MS could be encouraged and supported by, for example:</p> <ul style="list-style-type: none"> • The organisation of an EU-wide campaign to run alongside national campaigns; • The provision of support from the Commission for mechanisms to increase the exchange of information and best practices during and after such campaigns; • Restrictions on advertising medicinal products known to pose a risk to or via the environment. <p>This option complements Option 19, regarding education and training of medical and veterinary staff.</p>			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> • Large audience, beyond health care professionals, scientific and policy communities • Awareness raising likely to generate behavioural changes in everyday practices • Examples of successful campaigns exist in Sweden and in France 		<ul style="list-style-type: none"> • Difficult to tailor messages to individuals or address questions and concerns from the public 	
Opportunities		Threats	
<ul style="list-style-type: none"> • General awareness raising of civil society could raise expectations regarding more sustainable design, production and use of pharmaceuticals 		<ul style="list-style-type: none"> • Inadequate resources in EU MS • Effectiveness could vary depending on design of campaigns and on cultural factors • Weak infrastructure to support better practices, e.g. inadequate functional take-back/collection schemes, little/no supervision of OTC or online purchasing 	
Further information			
<p>Successful examples in France include annual communication campaigns from Cyclamed, the eco-organisation in charge of the take-back schemes in place in pharmacies, which provide information about antibiotic consumption or more generally about use of medicines³⁹.</p> <p>Following the TV communication campaign organised by Cyclamed in July 2010, a 26% increase in</p>			

³⁹ www.sante.gouv.fr/les-medicaments-ne-les-prenez-pas-n-importe-comment.html

volumes collected in August 2010 compared to August 2009 was observed. The organisation of another communication campaign in 2013, which targeted the public (television, internet), health professionals (information letters, regional meetings) and institutions (through working groups, guidelines, partnerships), collected an additional 3.5% of unused medicines between 2012 and 2013 (ADEME, 2013; Cyclamed, 2013).

Selected references

Stakeholder consultation

ADEME (2013). *Médicaments : collections repères*. Paris.

Cyclamed (2013). *Rapport Annuel*.

EHFG (2011). *European Health Forum Gastein in Salzburg Medical University - Study on medicinal uses*.

Objective	Promoting sustainable use of pharmaceuticals	
Option 21: Develop recommendations or requirements regarding the size and form of packaging for pharmaceuticals to facilitate their efficient use		
Context		
<ul style="list-style-type: none"> • Packaging's main function is to protect the quality of the pharmaceutical product until its consumption. It also conveys key information about the product and contains detailed information sheets to ensure correct administration and use. • The size of medicinal product packages has become increasingly standardised, with fixed volumes or numbers of pills, although packaging sizes may vary between EU MS. Larger packages may result in over-supply, with the surplus generally being kept at home "in case", until the products are out of date and have to be discarded. Package sizes don't always match doctors' prescriptions, and generally assume that patients won't experience side-effects that cause them to change their treatment. • Furthermore, some pharmaceuticals are provided in packaging whose form does not allow surplus product to be used at a later date, even by the same patient, as it may have deteriorated or become contaminated (e.g. loose pills in a bottle). In some EU MS, unused pharmaceuticals returned to pharmacies before their expiry date were used under certain conditions to help their own population or countries in need (e.g. in France⁴⁰), but these practices were precluded after WHO's recommendations not support medicine waste 'recycling' because of questions relating to safety and traceability (WHO, 2010). 		
Description		
<p>This option aims at developing new recommendations or requirements regarding the packaging of pharmaceuticals to reduce the quantity of unused pharmaceuticals. These could be developed on the basis of, among other things:</p> <ul style="list-style-type: none"> • Surveying current practices with regard to packaging size/form and opportunities for the use of surplus pharmaceuticals in the EU and other countries; • Additional public consultation on the acceptability and value of such an option. <p>The recommendations/requirements might include suggestions or specifications for:</p> <ul style="list-style-type: none"> • The range of sizes of packages that should be available for certain types of pharmaceutical; • The types of packaging most suitable for certain types of pharmaceutical; • Information to be provided to pharmacists and patients in relation to the packaging size, including the possibility of making use of surplus pharmaceuticals. <p>A particular focus of the (statutory) impact assessment would be consideration of the overall costs and benefits, i.e. taking account of all aspects including costs relating to changes in the design/manufacture, the materials needed (more for single-dose forms?), handling costs and the transport involved.</p>		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Would be a welcome solution to the problem of wasted medicines • Would be supported by increasing trend towards marketing pharmaceuticals in single-dose forms where relevant • Successful examples in countries outside of the EU (e.g. USA) 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Little experience in the EU of using different packaging approaches 	

⁴⁰ <http://www.cyclamed.org/a-quelle-association-humanitaire-puis-je-donner-mes-medicaments-inutilises-2381>

<p>Opportunities</p> <ul style="list-style-type: none"> • Would provide scope to reduce healthcare costs linked to the reimbursement of unused medicines • Offers potential to improve patient safety, and would be consistent with 2015 Guidelines for the prudent use of antimicrobials in veterinary medicine 	<p>Threats</p> <ul style="list-style-type: none"> • Possible objections on the grounds of need for significant organisational changes (manufacturing, transport, storage, preparation skills in pharmacies) • Possible objections from patients unable or unwilling to return to the pharmacy to complete their course of treatment • Possible objections to utilising surplus pharmaceuticals on the grounds of risks to safety
<p>Further information</p>	
<p>Appropriate pack size could contribute to more appropriate use of antimicrobials. For example, the Commission Guidelines for the prudent use of antimicrobials in veterinary medicine (2015) includes the following: "The pack size and the strength of the available antimicrobial formulations should be adapted as far as possible to the approved indications of use, so as to avoid, for example, improper dosing and overuse."</p> <p>In the USA, many medicines are delivered to the patients by pharmacists in a package tailored to their prescriptions, with just the right amount for the duration of their treatment.</p>	
<p>Selected references</p>	
<p>Stakeholder consultation NoPills (2015) NoPills Final Report. Gauthier P. (2011). <i>Developing Drugs for Children and the Adjustment of Medication—Is It a New Challenge or an Adaptation of Past Ideas?</i> J Pers Med. 2011 Dec; 1(1): 5–16. European Commission (2015). <i>Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04)</i> WHO (2010). <i>Guidelines for medicines donations</i>. Revised version. http://apps.who.int/iris/bitstream/10665/44647/1/9789241501989_eng.pdf</p>	

Objective	Ensuring appropriate collection and disposal of unused pharmaceuticals and pharmaceutical waste	
Option 22: Promote better enforcement of EU legislation with regard to the implementation of waste collection schemes for human and veterinary pharmaceuticals, including through extended producer responsibility		
Context		
<ul style="list-style-type: none"> • Since 2004 for human pharmaceuticals⁴¹ (HMPs) and 2001 for veterinary pharmaceuticals⁴² (VMPs), all EU MS have been required to provide collection systems for unused pharmaceuticals. • Existing take-back schemes are managed at national, regional or local level depending on the country. They can be under the responsibility of publicly-owned companies or environmental non-profit organisations partly or fully financed by the industry through extended producer responsibility. • In 2010, in the majority of EU MS, a large share of unused medicinal products (from 50% up to 90%) were still not either separately collected or returned to pharmacies (EEA, 2010). • This low efficiency can be explained by three main issues: <ul style="list-style-type: none"> - The heterogeneous implementation of collection systems in EU MS: whereas take-back schemes are relatively well organised for HMPs, collection of VMPs remains informal in several EU MS (they are collected together with other types of veterinary waste by veterinarians or directly disposed of in the municipal waste stream); - A lack of disposal and collection points: for HMPs, the collection is mostly ensured by pharmacists. In some countries, this collection is only made on a voluntary basis: not all accept unused medicines and a few discourage this practice. Sharp medical waste (needles, syringes) and veterinary medicines are accepted by pharmacies only in a limited number of EU MS; - A lack of awareness among the general public: experience demonstrates that patients with knowledge about the impact of pharmaceuticals in the environment were more likely to return pharmaceuticals for proper disposal. 		
Description		
<p>This option aims at:</p> <ul style="list-style-type: none"> • Establishing practical guidance on the implementation/improvement and assessment of collection schemes for unused pharmaceuticals, based on success stories (e.g. from pharmacies, hospitals or healthcare centres); • Encouraging EU MS to monitor and report on their efficiency; • Promoting relevant examples of successful financing mechanisms, e.g. through producer extended responsibility. <p>It complements Option 20, which covers the issue of awareness-raising among consumers, and Option 21, which addresses to some extent the possibility of using rather than destroying collected pharmaceuticals, which could motivate some patients to return them before expiry.</p>		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Better transparency and clarity of collection schemes across EU MS • Better support for the implementation of take-back schemes and improvement of their efficiency • Existing success stories in EU MS for HMPs, and to a lesser extent for VMPs 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Reliant on national legislation to establish responsibilities for pharmaceutical waste collection • Lack of in-depth assessments of existing scheme effectiveness (estimated recovery rate of unused/expired drugs) in many EU MS • Schemes may not be able to pay for themselves 	

⁴¹ [Directive 2001/83/EC](#) and in [Regulation \(EC\) No 726/2004](#)

⁴² [Directive 2011/82/EC](#)

<p>Opportunities</p> <ul style="list-style-type: none"> • Can build on systems already in place in most countries • Scope to tailor packaging (e.g. blister vs. bottles) to allow unused medicines to be reallocated for use once collected (and to promote this benefit of collection systems) • Scope to promote as a way of contributing to the prevention of unsafe storage practices and drug abuse 	<p>Threats</p> <ul style="list-style-type: none"> • Uncertain implementation of (non-binding) guidelines • Possible failure to engage the general public • Possible failure to engage pharmacists or collectors on a voluntary basis, especially if no support in place to receive collected pharmaceuticals • Some EU MS, such as Germany, may prefer to recommend disposal of unused medicines into municipal waste for incineration – but what about non-expired pharmaceuticals and liquids?
Further information	
<p>Meds-Disposal is a campaign to raise awareness on how to dispose of unused or expired medicines appropriately in Europe, presenting information on current disposal schemes in EU MS. It is a joint initiative between European healthcare, industry and student organisations (http://medsdisposal.eu).</p>	
Selected references	
<p>Stakeholder consultation</p> <p>EEA (2010). <i>Pharmaceuticals in the environment</i>. Technical report No 1/2010. Available at: www.eea.europa.eu/publications/pharmaceuticals-in-the-environment-result-of-an-eea-workshop</p> <p>EurEau's Contribution to the European Commission Strategic Approach on Pharmaceuticals in the Environment, http://eureau.org/administrator/components/com_europublication/pdf/d127f8273bad53d568242fdc3a3c9f26-2014.05.26_PP_on_Pharmaceuticals.pdf</p> <p>Fenech C., Rock L., Nolan K., Morrissey A. (2013). <i>Attitudes towards the use and disposal of unused medications in two European Countries</i>. <i>Waste Management</i> 33. 259–261</p> <p>HCWH (2013). <i>Unused Pharmaceuticals Where Do They End Up? A Snapshot of European Collection Schemes</i>, 2013, https://noharm-europe.org/documents/unused-pharmaceuticals-where-do-they-end-snapshot-european-collection-schemes</p> <p>Meds-Disposal: http://medsdisposal.eu/.</p> <p>NoPills (2015). <i>NoPills Final Report</i>.</p> <p>Roig, B. (2010). <i>Pharmaceuticals in the Environment: Current Knowledge and Need. Assessment to reduce presence and impacts</i>.</p> <p>Tong, AY., Peake, BM., Braund, R. (2011). <i>Disposal practices for unused medications around the world</i>. <i>Environ Int.</i> 2011 Jan;37(1):292-8</p> <p>Velligna, A. et al. (2014). <i>Public practice regarding disposal of unused medicines in Ireland</i>. <i>Sci Total Environ.</i> 2014 Apr 15;478:98-102</p>	

Objective	Ensuring appropriate collection and disposal of unused pharmaceuticals and pharmaceutical waste
Option 23: Ensure that the CLP Regulation does not exclude pharmaceuticals in medicinal products and that its provisions are consistent with the Waste Framework Directive	
Context	
<ul style="list-style-type: none"> • The large majority of unused pharmaceuticals and waste contaminated by pharmaceuticals (e.g. packaging) is disposed of with municipal waste or directly in sewage. • Cytotoxic and cytostatic (anti-cancer) pharmaceuticals are the only pharmaceutical products explicitly classified as hazardous waste under the Waste Framework Directive⁴³. These hazardous substances require specific labelling, monitoring and control from the time of waste production to the time of final disposal. • The Waste Framework Directive allows EU MS to consider waste as hazardous even if it does not appear in the EU list, provided it displays relevant properties⁴⁴. However, to our knowledge, no Member State has, as yet, independently listed any other pharmaceuticals as hazardous. • Waste contaminated by pharmaceutical substances could be classified as hazardous waste in the following existing waste categories, if the pharmaceuticals (medicinal products) present in them were themselves classified as hazardous under the Classification, Labelling and Packaging (CLP) Regulation: sludge from on-site effluent treatment and solid waste containing dangerous substances, aqueous liquid wastes containing hazardous substances or chemicals consisting of or containing hazardous substances⁴⁵. • However, pharmaceuticals in the form of human and veterinary medicinal products are not considered dangerous substances under the CLP Regulation, since most are not in the scope of this Regulation⁴⁶. 	
Description	
<p>This option proposes to revise the CLP Regulation to remove the blanket exclusion of pharmaceuticals in the form of human and veterinary medicinal products: this would allow the classification of certain pharmaceuticals (in products) as dangerous to ensure that waste consisting of or containing them would be considered as hazardous waste and properly disposed of. The most relevant class of hazardous substance would be "hazardous to the aquatic environment". An alternative could be to add a specific reference/provision on pharmaceuticals in Annex III to the Waste Framework Directive on properties of waste which render them hazardous.</p> <p>More generally, information on disposal could be added to the product label.</p>	

⁴³ Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives, as amended by [Commission Regulation \(EU\) No 1357/2014](#).

⁴⁴ The Waste Framework Directive (2008/98/EC) defines hazardous waste as "waste which displays one or more of the hazardous properties listed in Annex III" (Article 3(2)).

⁴⁵ Wastes from the Manufacture Formulation Supply and Use of pharmaceuticals:

- 07 05 11* sludges from on-site effluent treatment containing dangerous substances
- 07 05 13* solid wastes containing dangerous substances
- 16 10 aqueous liquid wastes destined for off-site treatment
- 16 10 01* aqueous liquid wastes containing dangerous substances

Waste from human or animal health care and/or related research

- 18 01 06* chemicals consisting of or containing dangerous substances
- 18 01 08* cytotoxic and cytostatic medicines

Source: Commission Decision 2014/955/EU on the list of Waste

⁴⁶ Pharmaceutical substances and mixtures in the form of human and veterinary medicinal products, which are in a finished state, intended for the final user, are not included in the scope of the CLP Regulation.

Preliminary assessment	
<p>Strengths</p> <ul style="list-style-type: none"> • Proper disposal of all relevant pharmaceuticals • Exploits an established EU instrument, which is regularly updated (Annex IV of the CLP, listing dangerous substances) 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Administrative burden for regulatory agencies and manufacturers
<p>Opportunities</p> <ul style="list-style-type: none"> • Changes in CLP classification of hazardous substances further justified by the evolution of ecotoxicity criteria for the List of Waste: e.g. revision of the H14 criteria for ecotoxicity⁴⁷ 	<p>Threats</p> <ul style="list-style-type: none"> • Significant costs could result from classifying a substance as dangerous under the CLP Regulation, with implications for labelling, disposal as hazardous waste, and options for recovery⁴⁷ • Use of CLP labels (though not always needed for classified substances) could put patients off some pharmaceuticals even when they would be therapeutically advisable
Further information	
<p>An interesting initiative to highlight comes from the United States, where the hazardous waste regulations were recently revised (in 2015) and tailored to improve the management of hazardous waste pharmaceuticals by the healthcare sector, including healthcare facilities and pharmaceutical reverse distributors (in charge of pharmaceuticals collection or returns for disposal). The objective of this review was to make the regulations both more applicable and more effective in preventing emissions of pharmaceuticals into the environment, while pharmaceutical waste from this sector is very diverse and is generated at a large number of points in relatively small quantities across a facility (nursing stations, pharmacies, emergency and operating rooms)</p>	
Selected references	
<p><u>Legal basis</u> Directive 2008/98/EC & Commission Decision 2000/532/EC CLP Regulation on Classification, Packaging and Labelling of substances and mixtures (1272/2008) 2014/955/EU: Commission Decision of 18 December 2014 amending Decision 2000/532/EC on the list of waste pursuant to Directive 2008/98/EC of the European Parliament and of the Council Text with EEA relevance</p> <p><u>Other sources</u> Stakeholder consultation BIO by Deloitte, INERIS. (2015). <i>Study to assess the impacts of different classification approaches for hazard property "HP 14" on selected waste streams. For the European Commission – DG ENV.</i> European Commission - DG ENV. (2016, 06 07). <i>Hazardous Waste. Available at:</i> http://ec.europa.eu/environment/waste/hazardous_index.htm US Environmental Protection Agency. (2015). <i>Proposed Rule: Management Standards for Hazardous Waste Pharmaceuticals.</i> Récupéré sur https://www.epa.gov/hwgenerators/frequent-questions-about-management-standards-hazardous-waste-pharmaceuticals-proposed#q6 European Commission (2011). <i>Introduction to the CLP Regulation - The CLP Regulation & Pharmaceutical substances used in pharmaceutical compounding:</i> http://www.sacchiconsulting.com/CLP%20regulation%20and%20substances%20used%20in%20pharmaceutical%20compounding_Dr%20Klaus%20Berend.pdf.</p>	

⁴⁷ BIO by Deloitte, INERIS, 2015

Objective	Promoting more effective treatment of waste water, manure and sludge		
Option 24: Establish EU guidelines for appropriate wastewater management in hospitals and healthcare centres			
Context			
<ul style="list-style-type: none"> • So far there are no legislative requirements with regard to the release of pharmaceuticals into waste water networks. • Hospitals and healthcare centres generally make a very low contribution to total waste water discharges when compared to households (Herrmann et al., 2015) and a low contribution to the overall pharmaceutical environmental load (below 25%) (Kümmerer, 2010; Kümmerer, 2013; Ort et al., 2010; Le Corre et al., 2012; Helwig et al., 2013). This trend is strengthened by the increasing development of ambulatory care. • However, the contribution from hospitals can reach a much higher share as regards certain more hazardous pharmaceuticals and the prevalence of antimicrobial resistance bacteria for some categories of antimicrobials (e.g. Helwig et al., 2013; Santos et al., 2013). • A few hospitals have already successfully tested source segregation and pre-treatment of waste water in order to reduce pharmaceutical loads in water discharged to the municipal waste water system. 			
Description			
<p>The option aims at developing EU guidance for hospital/healthcare-centre managers in order to reduce contamination of municipal wastewater with residues resulting from the use and disposal of pharmaceuticals. This guidance would help them take decisions and practical action with regard to the safe collection, treatment and/or disposal of liquid waste contaminated by pharmaceuticals, from an environmental perspective, by highlighting best practices observed in some EU MS and their conditions of successful implementation. It could cover:</p> <ul style="list-style-type: none"> • Experience in source segregation to collect biological effluents, either from the whole hospital or from treated patients vs. non-treated patients, and pre-treatment of water; relevance to different types of hospitals/healthcare centres and departments; • Recommendations on how to liaise with water authorities for optimal wastewater treatment; • Recommendations on how to inform and provide relevant equipment for separate collection of contaminated waste to patients in ambulatory care (who are taking/excreting their medication outside of hospital or healthcare-centre premises). 			
Preliminary assessment			
<p>Strengths</p> <ul style="list-style-type: none"> • Pre-treatment of waste water could reduce/remove need for downstream UWWTP to remove certain hospital-specific pharmaceuticals • Separate collection of liquid waste in hospitals is increasingly common and managers/staff are often already familiar with it • Lessons have been learnt from front-runners and research projects on pre-treatment of wastewater 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Pre-treatment of wastewater from hospitals may be less effective than more upstream prevention options (e.g. because of the increase of ambulatory care) 		
<p>Opportunities</p> <ul style="list-style-type: none"> • Would exploit trend towards increased environmental awareness in waste management • Would increase awareness among the public of sustainable use of 	<p>Threats</p> <ul style="list-style-type: none"> • High infrastructure investment costs for wastewater treatment solutions • Adequate (advanced) waste water treatment (including monitoring) may be disproportionately expensive (including in 		

<p>pharmaceuticals</p> <ul style="list-style-type: none"> • Synergy with efforts to promote sustainability in the healthcare sector of hospitals and health-care centres as an asset for competitiveness 	<p>terms of energy, carbon) for the volumes handled. There might not be sufficient compensation from water companies.</p> <ul style="list-style-type: none"> • Costs related to personnel training and engagement in separate collection tasks • Difficulty in fostering acceptance of separation technologies in the hospital and at home by hospital staff and patients
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Further information

Relevant initiatives of source segregation for water pre-treatment already exist, such as:

- Danish Herlev Hospital - cleaning of hospital wastewater (DHI, 2016);
- Swedish Sahlgrenska hospital;
- Swedish Uppsala University hospital;
- Marienhospital in Gelsenkirchen (Germany) (noPILLS project);
- Centre Hospitalier Emile Mayrisch in Esch-sur-Alzette (Luxembourg) (noPILLS project).

On-site treatment from hospitals before discharge into public sewerage systems is recommended in the LIFE PharmDegrade project. RISKWA/SAUBER+ project also focuses on the Separate Treatment of Wastewater from Health Care Facilities.

Selected references

Stakeholder consultation

DHI (2016). *Full scale advanced wastewater treatment at Herlev hospital – Treatment performance and evaluation*, Grundfos BioBooster A/S Report. May 2016

Helwig et al. (2016). *Ranking prescribed pharmaceuticals in terms of environmental risk: inclusion of hospital data and the importance of regular review*. Environmental Toxicology and Chemistry.

Herrmann, M., Olsson, O., Fiehn, R., Herrel, M. & Kümmerer, K. (2015). *The significance of different health institutions and their respective contributions of active pharmaceutical ingredients to wastewater*. Environment International, 85, pp.61-76. DOI: 10.1016/j.envint.2015.07.020

IFAT (2012). *Full-scale plant for the elimination of pharmaceuticals in hospital wastewater – Comparison of advanced treatment technologies. Case study from the pilot plan of the Marienhospital. 16th International EWA Symposium, Munich, 8th-9th May*

Kümmerer, K. (2010). *Pharmaceuticals in the environment*. Annu. Rev. Environ. Resour. 35 (1), 57-75

Kümmerer, K. (2013). The issue of micropollutants in urban water management. In Source separation and decentralisation of wastewater management (p. 520).

Le Corre et al. (2012). *Consumption-based approach for assessing the contribution of hospitals towards the load of pharmaceutical residues in municipal wastewater*. Environ. Int. 45, 99 - 111.

LIFE PharmDegradeproject: Degradation of pharmaceuticals in wastewaters from nursing homes and hospitals September 2014 – November 2016. <http://lifepharmdegrade.arhel.si/>

NoPills (2015). *NoPills Final Report*.

http://www.nopills.eu/conference/BS_NoPills_Final%20Report_summary_EN.pdf

Ort et al. (2010). *Determining the fraction of pharmaceutical residues in wastewater originating from a hospital*. Water Res. 44 (2), 605 - 615.

RISKWA/SAUBER+ project: Innovative Concepts and Technologies for the Separate Treatment of Wastewater from Health Care Facilities. www.bmbf.riskwa.de/en/1282.php

Objective	Promoting more effective treatment of waste water, manure and sludge		
Option 25: Require monitoring of antimicrobials and AMR microorganisms in the effluent and organic waste from potential "hotspots" such as large waste water treatment plants, hospitals, manufacturing sites and intensive livestock farms			
Context			
<ul style="list-style-type: none"> • As noted in the context of Option 2, further research is needed to understand better the relationship between waste water discharges, manure/sewage sludge spreading, and AMR in the environment. • Relatively little is known about the prevalence of antimicrobials and AMR microorganisms in the above effluents and waste, because there are no specific requirements for monitoring them. • Certain hotspots – large waste water treatment plants, hospitals, antimicrobial manufacturing plants, and intensive livestock farms – could make a significant contribution to the discharges of antimicrobials and/or AMR microorganisms. • Additional monitoring data could make it easier to understand the role of such discharges in spreading AMR, and thus inform measures. 			
Description			
<p>This option aims at increasing the availability of monitoring data for antimicrobials and AMR microorganisms in the effluents from major facilities including large waste water treatment plants, hospitals and antimicrobial manufacturing sites, and in manure/sewage sludge from intensive livestock farms. This requires:</p> <ul style="list-style-type: none"> • Selecting the antimicrobials and the microorganisms in which AMR is to be monitored; • Identifying suitable hotspots for monitoring; • Ensuring that the monitoring is carried out for a sufficient period, if necessary by amending and/or introducing relevant legislation; • Establishing a, or exploiting an existing, reporting mechanism and carrying out analysis of the data. <p>It would be important to maximise use of existing sampling networks and routines.</p>			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> • Could exploit existing studies to identify suitable hotspots • Could exploit existing sampling networks 		<ul style="list-style-type: none"> • May require introduction of new legislation 	
Opportunities		Threats	
<ul style="list-style-type: none"> • Relevant to informing the development of the circular economy, e.g. water reuse • Relevant to the development of more efficient waste treatment 		<ul style="list-style-type: none"> • Additional information may be needed to understand which hotspots should be considered and which antimicrobials and microorganisms should be monitored. • Additional costs/resources to implement the additional monitoring requirements 	
Further information			
<ul style="list-style-type: none"> • <u>Legal ground</u> The Urban Wastewater Treatment Directive (UWWTD) establishes minimum requirements for the collection, treatment and discharge of domestic wastewater or mixtures of urban wastewater and industrial waste water. It requires the performance of UWWTPs to be monitored, and the disposal and reuse of sewage sludge to be controlled, but the parameters to be monitored are generic parameters (e.g. biochemical oxygen demand, chemical oxygen demand, total suspended solids, indicators of eutrophication). 			

The Industrial Emissions Directive⁴⁸ covers pharmaceutical manufacturing facilities and some intensive farming facilities. In the frame of their permits, these facilities must ensure periodic monitoring of soil and groundwater in relation to relevant hazardous substances likely to be found on site and having regard to the possibility of soil and groundwater contamination at the site of the installation (Article 14 (e) of IED). Periodic monitoring shall be carried out at least once every 5 years for groundwater and 10 years for soil, unless such monitoring is based on a systematic appraisal of the risk of contamination (Article 16).

The list of examples below could inform the development of antimicrobials and AMR monitoring initiatives, although they are not all specific to AMR.

- Research projects on different water systems:

A few research projects specifically investigated AMR abundance from different wastewater systems, such as No Pills in Water (2015), RiskWa/SauberPlus, or COST Action.

- Examples of monitoring initiatives in Wastewater treatment plants:

In 2010, the JRC conducted an EU Wide Monitoring Survey on Waste Water Treatment Plant Effluents in collaboration with EU MS' environmental agencies and research centres. Effluents from 90 European waste water treatment plants (WWTPs) were collected and analysed in total for 160 organic chemicals and 20 inorganic trace elements, including pharmaceuticals (JRC, 2012).

A research initiative for AMR monitoring, part-funded by the European Regional Development Fund, was recently conducted in Spain. The researchers evaluated the abundance of antibiotic resistance genes in the Tordera River Basin in northern Spain, which receives input from domestic WWTPs. They looked for genes conferring resistance to major families of antibiotics in biofilm samples collected upstream and downstream of WWTP discharge points (Proia et al.).

Furthermore, in the Netherlands, the National Institute for Public Health and the Environment (RIVM) announced the drafting of an action plan for gaining better insight into the situation with regards to antibiotics resistance. Measurements in waste water from health facilities and residential areas, in waste water treatment plants and in manure, form part of this action plan (Ministry of Health, Welfare and Transport, 2016).

- Examples of monitoring initiatives in large manufacturing plants:

In their Eco-pharmaco stewardship Initiative, the Association of the European Self-Medication Industry (AESGP), European Federation of Pharmaceutical Industries and Associations (EFPIA) and Medicines for Europe promote the responsible management of manufacturing effluent. They recently supported the publication of an article on a risk-based approach to managing APIs in manufacturing effluent (Caldwell et al., 2016).

- Examples of monitoring initiatives in hospitals:

- In Sweden, the Västra-Götalands region launched a 2015-2017 research project to monitor antibiotic resistance at three major hospitals in the region (in collaboration with the Strama project - Swedish Strategic Program against Antibiotic Resistance).
- In Gothenburg, Sweden, Sahlgrenska hospital monitors pharmaceuticals in effluent from the Cancer Department. In Uppsala hospital, a pilot test has started focusing on toilet water in the infection department (IWA, 2016).
- Hermann et al. (2015) highlight the benefits of consumption-based approaches to predict APIs' respective contributions to wastewater effluents, therefore allowing to streamline monitoring efforts to target molecules. This could partially replace extensive monitoring campaigns for pollution.
- Research also exists to help design schemes for monitoring the most relevant pharmaceuticals in hospital effluents based on predicted concentrations and environmental toxicity data (Daouk et al., 2015; Helwig et al., 2016).

⁴⁸ See IED, Annex I, 5.3 (a), 5.3 (b) and 6.11

Selected references

Stakeholder consultation

Caldwell DJ et al. (2016). *A risk-based approach to managing active pharmaceutical ingredients in manufacturing effluent*. Environ Toxicol Chem. 2016 Apr;35(4):813-22.

COST Action: Detecting evolutionary hot spots of antibiotic resistances in Europe (DARE). www.cost.eu/COST_Actions/essem/TD0803

Daouk, S., et al. (2015). *Prioritisation methodology for the monitoring of active pharmaceutical ingredients in hospital effluents*. Journal of Environmental Management, 160, 324-332

European Commission (2016). *Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee of the Regions - Eighth Report on the Implementation Status and the Programmes for Implementation (as required by Article 17) of Council Directive 91/271/EEC concerning urban waste water treatment (COM/2016/0105 final)*.

Helwig et al. (2013). *Micro-pollutant point sources in the built environment: identification and monitoring of priority pharmaceutical substances in hospital effluents*. J. Environ. Anal. Toxicol. 3, 177.

Herrmann, M., Olsson, O., Fiehn, R., Herrel, M. & Kümmerer, K. (2015). *The significance of different health institutions and their respective contributions of active pharmaceutical ingredients to wastewater*. Environment International, 85, pp.61-76. DOI: 10.1016/j.envint.2015.07.020

IWA (2016). *Water and Pharmaceuticals – insights and perspectives for health and environment*. IWA Sweden Conference 2016.

JRC (2012). *EU Wide Monitoring Survey on Waste Water Treatment Plant Effluents*. JRC Scientific and Policy reports. <http://publications.jrc.ec.europa.eu/repository/bitstream/JRC76400/lb-na-25563-en.pdf.pdf>

Ministry of Health, Welfare and Transport in The Netherlands (2015) *Tackling Antibiotic Resistance*.

No Pills in water (2015). <http://www.no-pills.eu/?lang=fr>

Proia, L. et al. (2016). *Occurrence and persistence of antibiotic resistance genes in river biofilms after wastewater inputs in small rivers*. Environmental Pollution, 210, pp.121-128. DOI: 10.1016/j.envpol.2015.11.035

Pruden A. et al. (2016). *Management Options for Reducing the release of antibiotics and antibiotic resistance genes to the environment*. Environ Health Perspect. Volume 11. Issue 8. August 2013

RISKWA/SAUBER+ project: Innovative Concepts and Technologies for the Separate Treatment of Wastewater from Health Care Facilities. www.bmbf.riskwa.de/en/1282.php

Objective	Promoting more effective treatment of waste water, manure and sludge
Option 26: Develop EU funding opportunities for research, development and implementation of advanced water treatment technologies to ensure that levels of pharmaceuticals, including antibiotics, and of AMR microorganisms, are reduced	
Context	
<ul style="list-style-type: none"> • The effectiveness of waste water treatment at removing pharmaceuticals and their metabolites and degradation products remains highly variable, depending on the pharmaceutical, wastewater treatment process, and initial concentrations in the influent. Traces of several pharmaceuticals are detectable in effluents of wastewater treatment plants (WWTP) as well as in the receiving surface and groundwater. WWTPs are also sometimes identified as contributors to the development of AMR. • Advanced (tertiary) treatment technologies (e.g. ozonation, chlorination, ultraviolet (UV) radiation, membrane technologies, sand filters) are widely discussed as promising options for the mitigation of micro-pollutants (including pharmaceuticals and personal-care products) entering the aquatic environment. • Yet, these treatments are still very costly in terms of energy and materials, and disposal of sludge, and not consistent with the aim of preventing pollution by tackling the source; decision makers are also reluctant to invest in advanced waste water treatment if significant benefits for health and the environment cannot be demonstrated. • The tertiary technologies still require optimisation (e.g. to better deal with certain recalcitrant pollutants and the spread of AMR), and further work on how to make them more efficient. • The EU provides funding opportunities in the field of advanced water treatment through several programs and partnerships such as: Horizon 2020 Programme, the European Innovation Partnership on Water (EIP), the Joint Programming Initiative (JPI) on Water and the Joint Programming Initiative on Antimicrobial Resistance. • The EU also offers funding opportunities under the European Structural and Investment Funds (ESIF⁴⁹), and in particular under the European Regional Development Fund and the Cohesion Fund for the construction of wastewater treatment plants. 	
Description	
<p>The aim of this option is to increase funding opportunities to develop and implement advanced treatment technologies that allow the issue of pharmaceuticals and AMR microorganisms in waste water to be efficiently tackled by:</p> <ul style="list-style-type: none"> • Improving clarity about the opportunities to develop and implement advanced treatment technologies under existing funds; • Devoting further resources to develop and implement advanced treatment technologies; and • Including a focus on pharmaceuticals and AMR in future research programmes and initiatives. <p>Because of the obvious links, this option could also cover technologies for better removal of pharmaceuticals and AMR microorganisms in the treatment of drinking water.</p>	

⁴⁹ The European Structural and Investment Funds (ESIF) include the European Regional Development Fund, European Social Fund, Cohesion Fund, European Agricultural Fund for Rural Development and European Maritime and Fisheries Fund.

Preliminary assessment	
<p>Strengths</p> <ul style="list-style-type: none"> • Additional scientific knowledge should assist the development of more efficient and competitive water treatment technologies • Existing funding programs for water treatment could be expanded 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Increased resource use in water treatment, i.e. energy and materials/substances • Water treatment does not directly tackle the real source • May not be effective for future compounds
<p>Opportunities</p> <ul style="list-style-type: none"> • Projects can build on previous work on waste water treatment plants 	<p>Threats</p> <ul style="list-style-type: none"> • Requires high long-term investment • Some EU financing conditional upon policy implementation (not achieved in some MS) • Inadequate expertise to support funding applications
Further information	
<p><u>Examples of research projects funded by the EU:</u></p> <ul style="list-style-type: none"> • Under the H2020 programme, the PHARMA AD (2015-2017) project aims at Removing of pharmaceutical micro-pollutants from waste water by anaerobic digestion and its effect on nitrogen recovery from digestion by micro-algae. Another example is the POSEIDON project, already funded by the EU in the frame of the 5th Framework Program, which aimed at investigating wastewater and drinking water treatment with respect to their efficiency in eliminating PPCPs. The project was a success and the technologies have been applied in different treatment plants across the EU (Germany, Austria) (WEDECO, 2012). • Under the 2013 Water JPI Pilot Call on Emerging Contaminants, the projects FRAME (A novel Framework to Assess and Manage contaminants of Emerging concern in indirect potable reuse), MOTREM (Integrated processes for Monitoring and Treatment of Emerging contaminants for water reuse), PERSIST (Fate and Persistence of emerging contaminants and multi-resistant bacteria in a continuum of surface water groundwater) and Stare (Stopping Antibiotic Resistance Evolution) are directly relevant to pharmaceuticals and AMR in wastewater effluents. • The European Regional Development Fund and the Cohesion Fund shall support preserving and protecting the environment and promoting resource efficiency through investing in the water sector to meet the requirements of the Union's environmental acquis and to address needs, identified by the Member States, for investment going beyond those requirements". These include the construction of wastewater treatment plants. These funds are granted provided consistency with measures taken under the Water Framework Directive and compliance with key principles, such as the recovery of the costs of water services, which is mandatory to MS since the end of 2010. Priority is given to countries from the EU-13, which still have important needs in terms of ensuring the treatment of waste water, inter alia to ensure the achievement of 'good ecological status of all water bodies" (European Commission, 2014). <p><u>Examples of other relevant projects in the field:</u></p> <p>In the Netherlands, the project Pharmafilter involves a water treatment plant handling hospital waste to ensure the complete degradation of pharmaceuticals with the use of advanced treatment (advanced oxidation). The project was financed by private industries and the Dutch government and supported by European Water and Life+ Framework funding (stowa, 2013).</p> <p>In Sweden, the following projects aim at improving wastewater treatments in hospitals:</p> <ul style="list-style-type: none"> • Full scale advanced wastewater treatment at Herlev Hospital (DHI, 2016); • Mermis project tested in the Aarhus University Hospital, based on the Moving Bed Biofilm Reactor (MBBR) technology (Mermis - MUDP project, 2014-2017). 	

Selected references

Stakeholder consultation

DHI (2016). *Full scale advanced wastewater treatment at Herlev hospital – Treatment performance and evaluation*, Grundfos BioBooster A/S Report. May 2016

EIP Water: European Innovation partnership on Water. <http://www.eip-water.eu/>

ESIF Funds: http://ec.europa.eu/contracts_grants/funds_en.htm

European Commission (2014). *Draft thematic guidance fiche for Desk Officers – Water management - VERSION 2 - 20/02/2014*.

http://ec.europa.eu/regional_policy/sources/docgener/informat/2014/guidance_2_thematic_objective_6_water_management.pdf

European Commission (2016). *Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the regions - Eighth Report on the Implementation of the Urban Waste Water Treatment Directive (91/271/EEC) -*

http://ec.europa.eu/environment/water/water-urbanwaste/implementation/implementationreports_en.htm

European Court of Auditors. (2015). *EU funding of urban waste water treatment plants in the Danube river basin: further efforts needed in helping Member States to achieve EU waste water policy objectives*. http://www.eca.europa.eu/Lists/ECADocuments/SR15_02/SR_DANUBE_RIVER_EN.pdf

Kümmerer, K. (2013). *The issue of micropollutants in urban water management*.

Mermis - MUDP project (2014-2017). *Environmentally friendly treatment of highly potent pharmaceuticals in hospital wastewater*.

PHARMA AD project (2015-2017). *Removal of pharmaceutical micro-pollutants from waste water by anaerobic digestion and its effect on nitrogen recovery from digestate by micro-algae*.

http://cordis.europa.eu/project/rcn/196095_en.html

Stowa (2013). *Evaluation report Pharmafilter*.

<https://www.reinierdegraaf.nl/rdgg/cache/file/507BD2BF-CC1D-42DA-A8577060EA03636E.pdf>

Joint Programming Initiative on Antimicrobial Resistance: <http://www.jpamr.eu/>

Joint Programming Initiative on water:

http://www.waterjpi.eu/index.php?option=com_content&view=article&id=202&Itemid=682; Page on call for proposals regarding Emerging contaminants in water:

http://www.waterjpi.eu/index.php?option=com_content&view=article&id=324:water-jpi-pilot-call-seven-projects-recommended-for-funding&catid=94:press-releases&Itemid=703

POSEIDON project FP5 (2004). *Assessment of Technologies for the Removal of Pharmaceuticals and Personal Care Products in Sewage and Drinking Water Facilities to Improve the Indirect Potable Water Reuse*. <http://www.eu-poseidon.com>

WEDECO (2012). *Ozone Wastewater treatment*. <http://www.xylemwatersolutions.com/scs/uk/en-gb/brands/wedeco/Documents/Ozone%20Wastewater%20Treatment.pdf>

World Health Organisation (2014). *Safe management of wastes from health-care activities*.

Objective	Promoting more effective treatment of waste water, manure and sludge	
Option 27: Encourage Member States to establish innovative mechanisms for investing in advanced (waste and drinking) water treatment		
Context		
<ul style="list-style-type: none"> • As noted in the context of Option 26, advanced waste water treatment requires high investment. If transferred to the user, costs could increase by 18 to 70 € per person/per year, depending on the technology used, on the size of the plant and on the removal rate of pharmaceuticals (EurEau, 2014). • At EU level, funds are available to support the construction of advanced water treatment plants (e.g. Cohesion Fund (CF), European Structural and Investment Funds (ESIF), but the funding is limited, and is subject to certain conditions so may not immediately be available. Therefore MS may themselves need to consider providing incentives for innovative finance. 		
Description		
<p>This option aims at encouraging EU MS to incentivise finance for the implementation of advanced waste and drinking water treatment systems.</p> <p>The European Commission could contribute by:</p> <ul style="list-style-type: none"> • Conducting and disseminating a study; • Sharing and discussing the results in a workshop for MS authorities. <p>The study could cover several possible ways for MS to incentivise new treatment schemes, such as:</p> <ul style="list-style-type: none"> • Encouraging MS to identify relevant pharmaceuticals as River Basin Specific Pollutants under the Water Framework Directive, establishing appropriate permitting and imposing fines for non-compliance, to be diverted into upgrading treatment plants; • Exploring funding options linked with the implementation of extended producer responsibility; • Provision of information to the public of the benefits of advanced treatment, and upward revision of water tariffs for consumers (increased revenue to be used for upgrading plants); • Public-private partnerships. <p>It would be important to take into account the relevance of pollution from other chemical substances, and the need to share the burden of upgrade costs appropriately.</p>		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Possibility of inspiring new financial mechanisms/investment streams • Can build on experiences, and best practices from MS which have made significant progress in the development of advanced treatment techniques (Switzerland, Germany and Sweden) • Diversity of possible financial mechanisms adapted to different MS conditions, diversity of actors (private, public, consumer, industry) and thus funds • Linking financing to a charge to polluters (industry/consumers) would partly implement the polluter-pays and cost-recovery principles (similar to the conditions for ESIF and CF financing) 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Increased resource use in water treatment, i.e. energy and materials/substances • Water treatment does not directly tackle the real source • May not be effective for future compounds 	

<p>Opportunities</p> <ul style="list-style-type: none"> • EU MS able to assess the best-suited financial mechanisms <ul style="list-style-type: none"> - Potential additional support with the EU funds to ensure efficient advanced treatments - Potential applications for water reuse in countries with regular water shortages 	<p>Threats</p> <ul style="list-style-type: none"> • Requires high long-term investment Private investors need in-depth assessment of the profitability of advanced waste water treatment, which may not be easy to predict • Incomplete implementation of UWWTD and Drinking Water Directive in several Member States; therefore their priority is establishing basic UWWT infrastructure • Costs may not be acceptable to consumers, especially if profits go to private companies
Further information	
<p><u>Examples of financial strategies observed in Europe and globally:</u></p> <ul style="list-style-type: none"> • Switzerland is one of the first countries to start implementing a national policy to reduce micropollutants in the effluents of municipal sewage treatment plants (STPs). To eliminate micropollutants caused by phytosanitary products in agriculture, this country decided to add a new step in the treatment of waste water in more than a hundred plants. This upgrade will be financed by households and industries through a federal tax for waste water, included in the 2014 revision of the Swiss federal law on the protection of water. This tax will not exceed CHF 9 per capita per year and will be withdrawn by 2040 at the latest (LEaux, 2014). Annual costs for upgrading 123 STPs are estimated at CHF 133 million (US\$ 97 million) or CHF 86 (US\$ 63) per household connected to these STPs. This is in line with the average willingness to pay per household is CHF 100 (US\$ 73) annually for reducing the potential environmental risk of MPs to a low level (Logar et al., 2014). • Another strategy highlighted by some private and non-governmental organisations would involve a fee that could be added to the cost of pharmaceuticals to pay for their collection/disposal/treatment Invalid source specified.. 	
Selected references	
<p>Stakeholder consultation</p> <p>LEaux (2014). <i>Loi fédérale sur la protection des eaux. Modification du 21 mars 2014.</i> https://www.admin.ch/opc/fr/official-compilation/2014/3327.pdf</p> <p>Logar, I. (2014). <i>Cost-benefit analysis of the Swiss national policy on reducing micropollutants in treated wastewater.</i> Environ Sci Technol. 2014 Nov 4;48(21):12500-8. doi: 10.1021/es502338j. Epub 2014 Oct 17.</p>	

Objective	Promoting more effective treatment of waste water, manure and sludge	
Option 28: Take additional measures, e.g. set quality standards or risk assessment requirements, to ensure that the concentrations of relevant pharmaceuticals and AMR microorganisms in manure, sewage sludge, and irrigation water are safe before it can be spread on agricultural fields		
Context		
<ul style="list-style-type: none"> • In the EU, sewage sludge and manure are regularly used to amend agricultural soils and waste water can be used for irrigation purposes. However, they have been found to contain a number of contaminants, including a variety of pharmaceuticals that could contaminate the soil and contribute to the spread of AMR. • The level of pharmaceuticals in manure, sewage sludge and irrigation water applied to agricultural fields is not regulated in the EU: <ul style="list-style-type: none"> - The current Fertilisers Regulation, which regulates the quality of fertilisers placed on the EU market, only applies to inorganic fertilisers. A proposal under negotiation aims to extend it to organic fertilisers, but no mention is made of potential contamination by pharmaceuticals or AMR microorganisms; - The Sewage Sludge Directive focuses mainly on limit values for heavy metals in soil; - The UWWTD does not regulate the pharmaceutical content of treated waste water and there is currently no EU regulation regarding the quality of water used for irrigation purposes, regardless of its source, although the European Commission is currently working on a limited set of standards for waste water for reuse; - Pharmaceuticals are exempted from the monitoring and setting of emissions levels set for the intensive rearing of poultry and pigs under the Industrial Emission Directive (IED). • For precautionary reasons, some EU MS forbid the use of manure and sewage sludge because of the risks potentially posed by pollutants, including pharmaceuticals. They thus lose the potential benefit of being able to use these resources to amend soils or for irrigation purposes. • The Circular Economy Action Plan published in December 2015 by the European Commission includes actions on reuse, including the development of legislation on minimum quality requirements for water reuse to be proposed in 2017 (EC, 2015). 		
Description		
<p>This option aims to ensure that manure, sewage sludge and water used as fertilisers or for irrigation, respectively, are safe. This might be done 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.</p> <p>It would require:</p> <ul style="list-style-type: none"> • Improved characterisation of risks linked with the reuse of waste water for irrigation as compared with other sources of irrigation water; • A technical investigation of the feasibility of setting concentration limits at EU level for manure, sewage sludge and irrigation water as appropriate, and a review of best practices to reduce contamination by pharmaceuticals and AMR microorganisms (e.g. delay before application of manure); • Possible amendment of the Fertilisers Regulation, the Sewage Sludge Directive, and/or Best available technique reference document on the intensive rearing of poultry and pigs; • Possible inclusion/development of provisions on using manure from cattle and other intensively farmed animals and/or on waste water reuse in actions under the Circular Economy Package. These could include, for example, the promotion of biogas production. 		
Preliminary assessment		
Strengths <ul style="list-style-type: none"> • Technical feasibility exists to reduce contamination of manure/sewage sludge by 	Weaknesses <ul style="list-style-type: none"> • Incomplete elimination of AMR bacteria following current treatment of sludge and 	

<p>pharmaceuticals through digestion and composting at relatively low costs (still uncertainties with regards to AMR)</p> <ul style="list-style-type: none"> • Could be supported by limited amendment of existing policy instruments 	<p>waste water and risk of emergence due to concentrations of antimicrobials</p> <ul style="list-style-type: none"> • Knowledge gaps on the emergence and spread of AMR and efficiency of mitigation practices • Lack of data and tests for assessing and defining safe concentration limits
<p>Opportunities</p> <ul style="list-style-type: none"> • Could assist farmers with not overstepping storage capacity for livestock manure under the Nitrates Directive 	<p>Threats</p> <ul style="list-style-type: none"> • Cultural differences in EU MS • Need better assessment of potential health benefits to justify additional administrative burden

Further information

Reuse of sludge or organic fertilisers for agricultural purposes:

Some EU MS have already implemented legislation to limit the use of sludge or organic fertilisers based on potential risks posed by pollutants, including pharmaceuticals. In Germany, this is the case in Bavaria and Nordrhein-Westphalia.

At EU level, an ad-hoc task group on water reuse was established in the CIS Work Programme 2016-2018. The group has developed guidelines on re-use, and the JRC is currently working on a technical report to support the development of a proposal for minimum quality requirements for water reuse in agricultural irrigation and aquifer recharge. The proposal will be subject to impact assessment. The European Commission is also conducting a public consultation on the most relevant options to maximise water reuse (see CIRCA BC Platform for water reuse and internet page).

Reuse of sludge, manure and other organic waste for biogas production:

According to Recital 12 of the Renewable Energy Directive 2009/28/EC: "The use of agricultural material such as manure, slurry and other animal and organic waste for biogas production has, in view of the high greenhouse gas emission saving potential, significant environmental advantages in terms of heat and power production and its use as biofuel. Biogas installations can, as a result of their decentralised nature and the regional investment structure, contribute significantly to sustainable development in rural areas and offer farmers new income opportunities."

Selected references

Legal basis

Fertilisers Regulation - European Commission (2016) COM(2016) 157 final - Proposal for a Regulation of the European Parliament and of the Council laying down rules on the making available on the market of CE marked fertilising products and amending Regulations (EC) No 1069/2009 and (EC) No 1107/2009

Sewage Sludge Directive - Council Directive 86/278/EEC of 12 June 1986 on the protection of the environment, and in particular of the soil, when sewage sludge is used in agriculture

BREF on intensive rearing of poultry and pigs (<http://eippcb.jrc.ec.europa.eu/reference/irpp.html>)

Other sources

Stakeholder consultation

CIRCABC Platform on water reuse: <https://circabc.europa.eu/w/browse/657861df-abc2-4d8a-bb4a-227e12c72dad>

European Commission internet page on water reuse: <http://ec.europa.eu/environment/water/reuse.htm>

European Commission (2015). *Closing the loop – An EU action plan for the circular economy*. http://eur-lex.europa.eu/resource.html?uri=cellar:8a8ef5e8-99a0-11e5-b3b7-01aa75ed71a1.0012.02/DOC_1&format=PDF

Prosser et al. (2015). *Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation*. *Environment international*, 75, 223-233 (including corrigendum).

UBA (2015). Website: <https://www.umweltbundesamt.de/en/topics/soil-agriculture/ecological-impact-of-farming/pharmaceuticals>

Youngquist et al. (2016). *Fate of antibiotics and antibiotic resistance during digestion and composting:*

A review. *Journal of Environmental Quality*, 45(2), 537-545.

Objective	Promoting more effective treatment of waste water, manure and sludge	
Option 29: Encourage Member States to revise their Codes of Good Agricultural Practice and revise relevant best available techniques under the IED at EU level to include provisions for the handling of manure containing pharmaceuticals/AMR microorganisms		
Context		
<ul style="list-style-type: none"> • The use of manure as fertiliser is widespread in the EU, although differences in the extent of intensive livestock farming make it more relevant in some EU MS than others. • Manure containing antimicrobials and AMR microorganisms can pose a risk of water and soil pollution (Graham, 2016, Hartmann, 2013) and AMR can be spread via the food chain. It has been shown that the frequency of bacteria carrying anti-microbial resistant genes (to amoxicillin and tetracycline) is higher for pigs (which use high amounts of antibiotics) as compared to cattle or sheep (Heuer, 2011). • A number of manure management practices allow the risk of antimicrobial contamination and contamination by AMR genes to be reduced (e.g. storage, digestion and composting). However, the efficiency of elimination remains variable and there is still a risk of emergence and spread of AMR microorganisms during storage, due to selective pressure or the natural transfer of resistant genes. • Yet, this issue is still little promoted and connected with agricultural policies in the EU, such as the Common Agricultural Policy, the national Codes of Good Agricultural Practice developed under the Nitrates Directive or measures related to pesticides, despite several opportunities for synergies. • At EU level, under the Industrial Emission Directive (IED), there is no Best Available Techniques Reference Document (BREF) for cattle. BREF applying to intensive rearing of poultry and pigs mentions the issue of pharmaceuticals emissions to water and soils, including possible risks of spread of AMR. Some of the Best available techniques (BAT) for storage, processing and application of manure may be relevant to limiting contamination of soils and water by pharmaceuticals and in particular by antimicrobials as well as limiting the spread of antimicrobial resistant pathogens, beyond their focus on nutrients and heavy metals. Yet, more clarity regarding these synergies and current gaps is needed. Furthermore, there are no BAT conclusions for the moment for the intensive rearing of poultry and pigs, only a BREF, which is not binding as such. 		
Description		
<p>This option aims at promoting new techniques of manure management at national and European scales through:</p> <ul style="list-style-type: none"> • The development of best manure handling practices under the IED, within the BREF for intensive rearing of poultry and pigs; • Development of such practices for manure from cattle and other intensively farmed animals; • The integration of these practices in current Codes of Good Agricultural Practice (GAP) implemented at national level. 		
Preliminary assessment		
<p>Strengths</p> <ul style="list-style-type: none"> • Technical feasibility exists to reduce contamination of manure/sewage sludge by pharmaceuticals through digestion and composting at relatively low costs (still uncertainties with regards to AMR) • Able to build on existing BAT and GAP codes 	<p>Weaknesses</p> <ul style="list-style-type: none"> • MS are not equally concerned since manure handling depends on the amount of livestock farming in the country • Knowledge gaps on the emergence and spread of AMR and efficiency of mitigation practices in the field of manure management 	

<p>Opportunities</p> <ul style="list-style-type: none"> • Potential synergies with nutrient and micro pollutant (e.g. heavy metals) management strategies 	<p>Threats</p> <ul style="list-style-type: none"> • Could be difficult to determine how to share costs between actors (farmers, water companies, consumers, etc.) • Infrastructure: the majority of the holdings with livestock in the EU-28 still lack storage facilities for manure
<p>Further information</p>	
<ul style="list-style-type: none"> • Composting and anaerobic digestion are practices already identified as able to significantly reduce levels of pharmaceuticals in manure in nearly all cases. There is more limited evidence regarding their impacts on levels of AMR microorganisms (Youngquist et al., 2016; Massé et al., 2014). The degradation of pharmaceuticals through composting has also been shown for sewage sludge (Haiba et al., 2013). • However these techniques still need to be optimised and/or complemented by other practices or technologies to ensure fully sufficient removal of pharmaceuticals. For instance, practices of source segregation can be applied such as antibiotic collection by absorbent materials before manure is spread onto land. 	
<p>Selected references</p>	
<p><u>Legal ground</u></p> <p>BREF on intensive rearing of poultry and pigs (http://eippcb.jrc.ec.europa.eu/reference/irpp.html) Revised BREF on intensive rearing of poultry and pigs – Final draft. http://eippcb.jrc.ec.europa.eu/reference/BREF/IRPP_Final_Draft_082015_bw.pdf The Nitrates Directive – In brief: http://ec.europa.eu/environment/water/water-nitrates/index_en.html</p> <p><u>Other sources</u></p> <p>Stakeholder consultation Berkner S., K. S. (2014). <i>Antibiotic resistance and the environment - there and back again</i>. Massé et al. (2014). Potential of Biological Processes to Eliminate Antibiotics in Livestock Manure: An Overview. O'Neil, J. (2015). <i>Antimicrobials in Agriculture and the Environment: Reducing Unnecessary use and waste. The Review on Antimicrobial Resistance</i> Prosser et al. (2015). <i>Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation</i>. Environment International, 75, 223-233 (including corrigendum). Pruden A. (2013). <i>Management options for reducing the release of Antibiotics and Antibiotic Resistance Genes to the Environment</i>. Haiba et al. (2013). <i>Degradation of some pharmaceuticals during sewage sludge composting</i>. Global Journal on Advances Pure and Applied Sciences, Vol 1 (2013) Youngquist, C. et al. (2016). <i>Fate of antibiotics and antibiotic resistance during digestion and composting: A review</i>. Journal of Environmental Quality, 45(2), 537-545.</p>	

Objective	Promoting better management of pharmaceutical emissions into soils and the aquatic environment		
Option 30: Prepare guidance under the Common Implementation Strategy (CIS) for the Water Framework Directive (WFD) to support better Member State action against pharmaceuticals in the aquatic environment			
Context			
<ul style="list-style-type: none"> • The Common Implementation Strategy (CIS) coordinates efforts to reach the objectives of the WFD. It promotes the implementation of measures addressing chemical pollution, in particular by way of the activities of the Working Group on Chemical aspects but also that of the Working Group on Groundwater. The current 2016-2018 CIS work program mentions the need for Working Group Chemicals to be involved in/be consulted on the development of the Strategic approach to pharmaceuticals in the environment. • Many MS have begun taking action to manage pharmaceuticals in water. Others could benefit from their experience. • The strategic approach to pharmaceuticals is expected to be followed by proposals for measures, as appropriate. There may be scope to exploit synergies between the management of pharmaceuticals and the management of other micropollutants such as pesticides, biocides or other chemicals. 			
Description			
<p>This option aims to provide support to MS in their management of pharmaceutical substances in water. This could be done in the context of future Work Programmes of the Common Implementation Strategy, and include specific tasks such as:</p> <ul style="list-style-type: none"> • Developing guidance on different aspects of the strategic approach and (in due course, to follow up measures proposed on the basis of the approach) highlighting best practice and sources of information; • Holding workshops for MS authorities to enable them to share experience on how best to implement relevant measures and to identify the management options most appropriate for inclusion in their River Basin Management Plans (RBMPs); • Elaborating guidance on how to identify pharmaceuticals of national concern, e.g. via watch list monitoring or voluntary national campaigns, including tips on monitoring tools (including for screening). 			
Preliminary assessment			
Strengths		Weaknesses	
<ul style="list-style-type: none"> • Can be achieved using the existing tried and tested CIS mechanism and working groups • Lessons learnt from the implementation of specific strategies and measures in some Member States and neighbouring countries (e.g. Sweden, France, Switzerland, Germany) 			
Opportunities		Threats	
<ul style="list-style-type: none"> • Synergies with work on watch lists for surface and groundwater • Potential synergies with WFD work on chemical mixtures 		<ul style="list-style-type: none"> • Resources needed to prepare guidance 	
Further information			
<p>Various EU-funded research project and national reports have highlighted initiatives taken in EU MS to address risks posed by pharmaceuticals in the environment. Some of these are likely to be relevant to following up the strategic approach and subsequent measures. EU projects of relevance include for instance: No Pills, TAPES or MistraPharma. Several EU MS and neighbouring countries are putting the issue of pharmaceuticals in the environment in their political agenda, such as Sweden with its 2016-2018 National Pharmaceutical Strategy (Lakemedelsverket, 2016), France with the 2010-2015</p>			

National plan on medicinal residues in water developed by the Health and Environment Ministries (PNRM, 2010-2015) and the recently launched MicroPol Strategy 2016-2021 (announced during the ICRAPHE conference 2016), Switzerland with the FOEN project «Micropollutants in Watercourses – MicroPoll Strategy” initiated in 2006 (FOEN, 2006), the CIPEL Micropollutant Strategy for the Lemane Lake (CIPEL, 2011-2020), or Germany at regional level (e.g. 2012 communication from the Reine Ruhr Commission and German Ministry of the Environment).

The CIS Working Group on Chemical Aspects has investigated the potential contribution of effect-based monitoring tools in the EU to make national monitoring programs more efficient (including reduction of monitoring costs). The use of effect-based tools in a WFD context can meet several objectives:

- Screening tools for prioritisation;
- Early warning systems;
- Consideration of the effects of chemical mixtures (e.g. to support investigative monitoring where causes of a decline of specific species are unknown).

Selected references

Stakeholder consultation

CIPEL (2011-2020). *Plan d'action 2011-2020 en faveur du Léman, du Rhône et de leurs affluents*. Commission Internationale pour la Protection des Eaux du Léman. 25 novembre 2010. http://www.cipel.org/wp-content/uploads/2012/04/pa_11-20_version_25-11-10.pdf

Common implementation strategy for the Water Framework Directive (2000/60/EC) and the Floods Directive (2007/60/EC) Work Programme 2016-2018: <http://ec.europa.eu/environment/water/water-framework/objectives/pdf/Work%20Programme%202016-2018.pdf>

European Commission (2014). *Technical report on aquatic effect-based monitoring tools*: <https://circabc.europa.eu/sd/a/0d78bbf7-76f0-43c1-8af2-6230436d759d/Effect-based%20tools%20CMEP%20report%20main%2028%20April%202014.pdf>

FOEN (2006). *Micropollutants in Watercourses – MicroPoll Strategy*.

Lakemedelsverket, (2016). *Swedish National Pharmaceutical Strategy 2016 – 2018*, <https://lakemedelsverket.se/upload/om-lakemedelsverket/NLS/The%20National%20Pharmaceutical%20Strategy%202016-2018.pdf>

MistraPharma (2008-2015). <http://www.mistrapharma.se/>

NoPills (2015). *No Pills in Water*. <http://www.no-pills.eu/?lang=fr>

PNRM 2010-2015. *Plan national des résidus de médicaments dans l'environnement*: <http://social-sante.gouv.fr/sante-et-environnement/les-plans-d-action-nationaux/article/plan-national-sur-les-residus-de-medicaments-dans-les-eaux-pnrm-2010-2015>

Reine Ruhr Commission (2012). *'Vom Programm 'Reine Ruhr' zur Strategie einer nachhaltigen Verbesserung der Gewässer- und Trinkwasserqualität'*. In partnership with Ministerium für Klimaschutz, Umwelt, Landwirtschaft, Natur- und Verbraucherschutz.

TAPES project: Transnational Action Program on Emerging Substances. <http://www.tapes-interreg.eu/>