Study on the environmental risks of medicinal products

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List of Acronyms

ADI	Acceptable Daily Intake
ADRs	Adverse Drug Reactions
AEMPS	Spanish Agency of Medicines and Medical Devices
AMDOPH	Drug metabolite
AMR	Antimicrobial Resistance
ANMV	French National Agency of Veterinary Pharmaceuticals (Agence Nationale du Médicament Vétérinaire)
ANSM	French National Agency of Pharmaceuticals Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé)
ANSES	French National Agency of Food, environment and work Safety (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail)
API	Active Pharmaceutical Ingredients
AQUAREF	Franch National Laboratory for the Monitoring of Aquatic Environment (Laboratoire National de Référence pour la Surveillance des Milieux Aquatiques)
ATC	Anatomical Therapeutic Chemical Classification System
BAT	Best Available Techniques
BREF	BAT Reference Document in the context of the Industrial Emissions Directive
CA	Concentration Addition
CESPharm	French Committee for the Social and Health Education of French Pharmaceutical sector (Comité d'Education Sanitaire et Sociale de la Pharmacie Française)
CHMP	Committee for Medicinal Products for Human Use - in the context of centralised EU market authorisation
CMR	Carcinogenic, Mutagenic and Reprotoxic
CMS	Concerned Member States
COM	Communication of the Commission
CPMP	European Committee for Proprietary Medicinal Products
CTC	Chlortetracycline
CVMP	Committee for Medicinal Products for Veterinary Use - in the context of centralised EU market authorisation
CYTOTHREAT	Fate and effects of cytostatic pharmaceuticals in the environment and

	identification of biomarkers for an improved risk assessment on environmental exposure
DDD	Defined Daily Dose
DNA	Deoxyribonucleic Acid
DOXI	Doxycycline hyclate
DS	Dry Solid
DRSP	Drospirenone
DT50	Degradation and Transformation or dissipation half-lives
DWEL	Drinking Water Equivalent Levels
EAHC	Executive Agency for Health and Consumers
E-PRTR	European Pollutant Release and Transfer Register
EC	European Commission
ECHA	European Chemical Agency
EC10	10% Effect Concentration
EC50	50% Effect Concentration
E2	Beta estradiol
EE2	Alpha ethinylestradiol
EEA	European Environment Agency
EFPIA	European Federation of Pharmaceutical industries and Associations
EICs	Environmental Introduction Concentrations
EMA	European Medicines Agency (formerly EMEA)
EMEA	European Agency for the Evaluation of Medicinal Products
EP	European Parliament
EPAR	European Public Assessment Report
EPC	European Patent Convention
EPR	Extended Producer Responsibility
EQSD	Environmental Quality Standards Directive (2008/105/EC)
ERA	Environmental Risk Assessment
ERAPharm	Environmental Risk Assessment of Pharmaceuticals
ESAC	European Surveillance of Antimicrobial Consumption
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
EVRA	Birth control Patch

FAO	Food and Agriculture Organization (of the United Nations)
FASS	Swedish environmental classification of pharmaceuticals
FOEN	Federal Office for the Environment in Switzerland
GABA	g-aminobutyric acid
GOW	General precautionary value (Gesundheitlicher Orientierungswert)
GMP	Good Manufacturing Practice
GREAT-ER	Geography Referenced Regional Exposure Assessment Tool for European Rivers
GWD	Groundwater Directive (2006/118/EC)
HBL	Health-Based Limit
HC_5	Hazardous Concentration for 5% of the species
HMG-COA	3-hydroxy-3-methyl-glutaryl-CoA reductase or HMGCR
HMP	Human Medicinal Products
IA	Independent Action of Pharmaceuticals
ICPE	Classified facilities for environmental protection (Installations Classées Pour la Protection de l'Environnement)
IED	Industrial Emissions Directive (2010/75/EU)
IGAS	General Direction for the Inspection of Social Affairs (Inspection Générale des Affaires Sociales)
IMI	Innovative Medicines Initiative
IMS Health	Intercontinental Marketing Services Health
IPPC	Integrated Pollution Prevention and Control (the IPPC Directive)
ISO	International Organisation for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JRC	Joint Research Centre of the EU
KNAPPE	Knowledge and Need Assessment on Pharmaceutical Product in Environmental Waters
K_{OC}	Soil Organic Carbon-Water Partitioning Coefficient
LIF	Swedish Association of the Pharmaceutical Industry (de forskande läkemedelsföretagen - länk till startsidan)
LLT	Type of MedDRA (Medical Dictionary for Regulatory Activities) coding
LoW	European List of Waste
LOEC	Lowest Observed Effect Concentration

LC	Life Cycle
LC50	50% Lethal Concentration
MA	Marketing Authorisation of medicinal products
MEC	Measured Environmental Concentration
MedDRA PT	Medical Dictionary for Regulatory Activities
MHRA	UK Medicines and Healthcare products Regulatory Agency
MPC	Maximum Permissible Concentrations
MRL	Maximum Residues Levels
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
MS	Member State of European Union
MSFD	Marine Strategy Framework Directive (2008/56/EC)
MFSU	Manufacture, Formulation, Supply and Use of medicinal products
MTD	Minimum Therapeutic Dose
NGO	Non-Governmental Organisation
NIEHS	UK National Institute of Environmental Health Sciences
NOEC	No Observed Effect Concentration
NORMAN	Network Of Reference Laboratories for Monitoring of Emerging Environmental Pollutants
NSAID	Non-Steroidal Anti-Inflammatory Drug
OECD	Organisation for Economic Co-operation and Development
OMS	Organisation Mondiale de la Santé (WHO)
OSPAR	Convention for the Protection of the Marine Environment of the North-East Atlantic
OTC	Used to define medicinal products sold Over The Counter
PAA	Public Administration Act in EU
PAR	Public Assessment Reports
PBT	Persistence, Bioaccumulation and Toxicity
PCU	Population correction Unit
PEC/PNEC	Risk Quotient between Predicted Environmental Concentration and Predicted Non-Effect Concentration
PEC	Predicted Environmental Concentration
PHARMAS	Ecological and human health risk assessment of antibiotics and anti-cancer drugs found in the environment

PhATE	Pharmaceutical Assessment and. Transport Evaluation Model
PL	Package Leaflet
PNEC	Predicted No-Effect Concentration
POSEIDON	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
PP	Polypropylene
PROTECT	The Pharmaco-epidemiological Research on Outcomes of Therapeutics by a European Consortium
QPhRA	Quantitative Pharmaceutical Risk Assessment
R&D	Research and Development
REACH	EU Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (1907/2006)
REMPHARMAWATER	Ecotoxicological assessments and removal technologies for pharmaceuticals in wastewaters
RIWA	Dutch Association of River Water Supply Companies
RMM	Risk Mitigation Measures
RMS	Reference Member State
RNA	Ribonucleic Acid
RQ	Risk Quotient
RSDE	Researching dangerous substances for water
SCOPUS	The world's largest abstract and citation database of peer-reviewed literature
SIGRE	Spanish pharmaceutical collection scheme
SPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
START	Pharmaceuticals for Human Use: Options of Action for Reducing the Contamination of Water Bodies.
STEP	Wastewater treatment plant (Station d'Epuration des Eaux Usées)(WWTP)
STP	Sewage Treatment Plant
SU	Standard Units
TDI	Total Daily Intake of a substance
TGD	Technical Guidance Document

TOC	Total Organic Carbon
TTC	Threshold of Toxicological Concern
TYL	Tylosin
UFs	Uncertainty Factors
UNECE	United Nations Economic Commission for Europe
US EPA	United States Environmental Protection Agency
UV	Ultraviolet
UWWTD	Urban Wastewater Treatment Directive (91/271/EEC)
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products
VMP	Veterinary Medicinal Products
VMD	Veterinary Medicines Directorate
WHO	World Health Organisation
WISE	Water Information System for Europe
WTW	Water Treatment Work
WWTP	Wastewater Treatment Plants

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Executive summary

The progress made by medical science during the last century and its positive impact on society are well known. Medicinal products are an important element of the medical practice and their beneficial effects (and side-effects) on human and veterinary health are widely acknowledged. However, the area where we lack a global view is understanding what happens when these medicinal products are discharged into the environment, either through consumption or as unused or expired products. Residues of various types of medicinal products (hormones, anti-cancer, antidepressants, antibiotics, etc.) have been detected in various environmental compartments, such as surface water, groundwater, soil, air, and biota. Such widespread occurrence obviously begs the question whether a concentration of medicinal products in the environment poses a risk for exposed biota or humans.

Recent pharmacovigilance legislation in the EU acknowledges that the pollution of waters and soils with pharmaceutical residues is an emerging environmental issue. The European Commission was asked to deliver a report on the scale of the issue, the causes, and possible policy options to mitigate such impacts. More recently, in the framework of the adoption of the Directive regarding priority substances in the field of water policy, the Commission has been asked to develop, instead of the report, a strategic approach to pollution of water by pharmaceutical substances by the end of 2015.

This study, together with other relevant studies and reports, will provide the basis to develop that strategic approach. The study covers both human and veterinary medicinal products but personal care products are excluded.

What is the scale of the issue?

During the last two decades, there has been an increasing trend in the R&D investments, industrial production, sale, and consumption of medicinal products in the EU. The EU market has grown from EUR 48 billion in 1990 to EUR 172 billion in 2007 and is expected to reach EUR 242 billion in 2014. In terms of market presence, around three thousand active pharmaceuticals ingredients (APIs) are currently authorised on the EU market as a whole, even if the APIs authorised at national level vary significantly.

For human medicinal products, the European Union (EU) is the second biggest consumer in the world (24% of the world total) after the United States of America. Consumption of human and veterinary medicines is quite heterogeneous across the EU Member States, for example, it ranges from 50 to 150 g/capita/year in the case of human medicinal products. Such heterogeneity is also reflected by the nature of the associated waste streams, which vary strongly in terms of quantities and/or quality, and pose a significant challenge for storage, collection and disposal of pharmaceutical waste. Moreover, in the majority of EU Member States, a large share of unused human medicinal products (50% on average) is not collected and some EU Member States do not implement take-back schemes.

How do medicinal products enter the environment?

The key steps (from an environmental perspective) in the life cycle of a medicinal product are manufacturing, consumption and waste management. Contamination pathways along the life cycle depend upon the life-cycle step during which the emissions occur. In the EU, the contribution of manufacturing facilities to emissions of medicinal products and/or their residues is generally considered as negligible, even though pollution downstream of manufacturing plants has been sporadically observed while monitoring specific sites (e.g. the Rhine, Lake Leman).

The consumption phase is considered to be the biggest contributor to the emissions of medicinal products into the environment, notably through excretions and incorrect disposal of unused medicines through sinks and toilets. Between 30 and 90% of the orally administered dose is generally excreted as active substance in the urine of animals and humans. However, the nature and amount of medicinal residues mainly depend on the volumes and nature of the administered substances, their modes of administration, and metabolisation rates. Medicinal products can also directly enter the environment through feed surplus, notably in the case of aquaculture: a recent survey measured up to 2.2 µg of teflubenzuron / kg of dry weight sediment coming from a marine fish farm in Scotland. Once in wastewater, treatment can partly eliminate or remove medicinal product residues, but some traces are still detectable in effluents as well as in the receiving surface and groundwaters. The residues remaining after wastewater treatment depend on the composition of the medicinal product, wastewater treatment process, and initial concentrations in the influent. For example, Ibuprofen, which is present in significant amounts in wastewater influents, is reduced by 60 to 96%, while Carbamazepine removal rates are much lower. As for landfills accepting medicinal products, sewage sludge can produce leachates containing concentrations similar to or even higher than those found in wastewater treatment plant influents.

How do medicinal products behave in the environment?

Once in the environment, medicinal products are transformed and transferred among different compartments, depending on the nature of the compounds and the characteristics of the host compartment. There exist voluntary initiatives for monitoring environmental concentrations of medicinal products in some Member States, particularly in the aquatic environment. These data suggest that several medicinal products are detectable in the environment, and their concentration depends on the geographical location, season, local administration practices, and specific environmental factors (T, humidity, etc.). The detected concentrations could be in the range of sub-ng/L levels to more than several µg/L.

Medicinal products can degrade biotically or abiotically in soils and water, a process that in general reduces their potency, even if some degradation products might be persistent and thus of concern. For instance, according to a monitoring campaign performed in France, the molecules most frequently found in freshwaters are Carbamazepine (an anti-epileptic medicinal product) and its main metabolite, and Oxazepam (an anxiolytic) which is both a parent product and a metabolite of

another pharmaceutical (Benzodiazepine). Highly lipid-soluble medicinal products may also have the ability to accumulate in the fat tissues of animals and can be thus introduced into the food chain (e.g. Ethynilestradiol could be a potential candidate for bioaccumulation in higher predators).

What kind of hazards and risks do they represent for ecosystems?

The mechanisms of transformations and transfer in the environment lead to the exposure of biota and constitute a potential risk for ecosystems. Although the scientific assessment of ecotoxicological effects of medicinal products on organisms is less developed compared to pesticides for example, it is becoming increasingly clear that some medicinal products, in particular anti-parasiticides, anti-mycotics, antibiotics and (xeno)estrogens, pose environmental risks in specific exposure scenarios. Examples of ecotoxicological effects of medicinal products include the contraceptive Ethinylestradiol, which impairs the reproduction of exposed fish populations; the effects of various antibiotics on environmental bacteria and algae; the impacts of the Benzodiazepine anxiolytic drug Oxazepam on European perch; and the effects of the anti-parasiticide Ivermectin on dung fauna. The decline of vulture populations on the Indian sub-continent due to poisoning with Diclofenac, a non-steroidal painkiller, is a good example of how unexpected exposure pathways – feeding on carcasses – can lead to severe ecotoxicological effects. For a range of other pharmaceuticals, environmental risks can be rather negligible, due to low environmental persistence and ecotoxicity of the compounds. In some cases, the data from human toxicology studies might help to provide read-across information on the potential effects on vertebrates, but many ecotoxicological modes of action are specific and the potential environmental effects cannot therefore always be extrapolated from human studies.

What are the potential impacts on human beings?

For humans, the possible impacts are less clear than for the environment, but there are concerns notably regarding certain type of molecules, even if to date there is no clear evidence of short-term health effects on humans. Antibiotics, anti-parasiticides, anti-mycotics and anti-cancer medicinal products are pharmaceutical groups that are especially intended to kill their target organism or target cells and might prove to be the most important pharmaceutical compounds affecting human health via environmental exposure. Chronic low-level exposure to medicinal products can occur through drinking water and through residues in leaf crops, root crops, fishery products, dairy products, and meat. The legislation in place for all veterinary medicinal products defines some Maximum Residue limits (MRL) for food of animal origin. However, to date no legal limit exists for human medicinal products potentially present in animal derived food (e.g. due to bioaccumulation from contaminated soil) since this pathway of exposure is assumed as negligible although the pathway is currently not well characterised.

Which factors influence the presence of medicinal products in the environment?

Several factors can influence the quantity and composition of the emissions to the environment, and/or the exposure levels of different ecosystems/human populations, thus finally determining the associated impacts. These factors can be of a legislative or non-legislative nature and influence the emissions during one or more life-cycle steps.

Legislative factors

- **Environmental Risk Assessment in the Market Authorisation (MA) process**

One of the key legislative factors influencing the presence of the medicinal products in the environment is the current framework for Environmental Risk Assessment (ERA), which is a part of the Market Authorisation process. For veterinary medicinal products, an ERA is required for all types of MA applications, including for new medicinal products, generics, variations and extensions, and is taken into account in a risk-benefit analysis in view of the authorisation. For several years, an ERA has also been required for a large number of human medicinal products on the market, but the ERA results in this specific case cannot lead to denying an authorisation, even if some Risk Mitigation Measures (RMM) can be required when considered necessary. In practice, there is a lack of ERA results for most human medicinal products currently consumed, as numerous active pharmaceutical ingredients contained in such medicinal products were authorised prior to 30 October 2005, which is when a proper ERA became an obligation for human medicinal products. The potential risks that 'old' pharmaceuticals may pose to the environment are therefore not properly assessed or not assessed at all. In addition, in the current ERA process, which is organised in three phases, not all medicinal products undergo a thorough environmental risk assessment, since the assessment of products fulfilling specific criteria stop after the first phase. APIs are often common among different medicinal products. However, since ERA information is built up on finished medicinal products and deemed confidential, data cannot be reused from one dossier to another, even if the concerned medicinal products contain the same API. This means that ERA results for the same active ingredient may be based on different endpoints depending on the concerned stakeholders, and may therefore differ from one product to another. Due to this approach, the subsequent ERA is not based on the real API's volumes emitted in the environment due to the sum of products, but only on a single product's share, which does not necessary reflect the environmental reality.

Similarly to ERA, a number of regulatory frameworks for chemicals commercialised and used in Europe, include an assessment for Persistence, Bioaccumulation and Toxicity (PBT) potential. Regarding veterinary medicinal products, no specific guidance is available on how to include this PBT assessment in the risk-benefit analysis or on which risk management measures would be needed in order to grant the MA. As for human medicinal products, similarly to the rest of ERA results, the output of the PBT assessment have up to now no consequences on MA, since it is not considered in the risk benefit analysis. However, risk management measures can be adopted in this respect when considered necessary.

Four procedures exist for the MA process: the three first procedures are Community procedures (centralised, decentralised and mutual recognition procedures), and the fourth is the national procedure which applies when the MA application is limited to the territory of one MS.

Under the centralised procedure, only the Committee in charge of the evaluation of veterinary medicinal products (CVMP) has a member appointed specifically due to his expertise on environmental risk assessment, while the one dedicated to human medicinal products (CHMP) does not necessarily include an environmental expert.

In the decentralised and mutual recognition procedures the level of ERA expertise and therefore the level at which an ERA is analysed depends in practice on the considered MS and is therefore very heterogeneous. This might lead in certain cases to parallel procedures for the same product followed in different (critical versus less critical) countries.

As reported by some MS, when looking at the output of the evaluation process, the ERA for human medicinal products is often incomplete or altogether absent from some MA applications. In these cases, the MA is therefore often granted with "post-marketing commitments" which are de facto not mandatory, since these results are not considered for the risk-benefit analysis and thus have no weight to obtain an MA.

When, based on the ERA results, a risk to the environment exists (whether for human or veterinary medicinal products), Risk Mitigation Measures (RMM) are recommended. In the case of veterinary medicinal products, information on potential environmental impacts must be taken into account in the pharmacovigilance system. However, compliance with RMM therefore has only a voluntary character, and their implementation is not systematically verified nor followed up on. Nonetheless, a Member State may suspend the use at a national level of a medicinal product for human or veterinary use, if urgent action is essential to protect human health or the environment.

Finally, environmental datasets produced in the context of ERA are often not publicly, or at least not easily, available. The level of accessibility might vary depending on the considered MS, but it is generally limited to risk assessors only and confidentiality reasons are invoked to justify the absence of publicly available datasets or their partial publication. When published, the quantity and quality of disclosed information vary depending on the type of procedure followed and on which MS was responsible for the evaluation (Reference Member State).

- **Other legislation**

Apart from the MA framework, a number of legislative texts could be relevant to address the issue of medicinal products in the environment at EU level. These include REACH, the Industrial Emissions Directive (IED), and the Water Framework Directive, among others.

Medicinal products are for the most part exempted from REACH requirements. They are, however, not exempted from the REACH provisions regarding restrictions on the manufacturing, placing on the market and use of certain dangerous substances and preparations. However, Annex XVII to REACH does not currently impose restrictions regarding active pharmaceutical ingredients. There are derogations for medicinal products from certain restrictions applicable to the use and placing on the market of carcinogenic, mutagenic and reprotoxic (CMR) substances as substances or in mixtures for supply to the general public; but restrictions could target certain active pharmaceutical ingredients, or the manufacturing process itself. A potential gap therefore lies in the fact that the EU legislation on medicinal products does not cover all lifecycle stages of the products (in particular

manufacturing and formulation), but at the same time medicinal products are exempted from many Titles under REACH.

The Industrial Emissions Directive (IED) applies to the medicinal products manufacturing sites, as well as to the sites of intensive rearing of poultry and pigs. However, even if APIs could fall within certain groups of water pollutants listed in Annex II, the IED does not yet include any active pharmaceutical ingredients in the list of polluting substances, and therefore does not set emission limit values nor require their monitoring.

EU legislation does not address the issue of soil contamination. Therefore, the issue of a soil contamination by medicinal products is not legally covered at EU level. The majority of the existing MS national soil legislation does not cover this specific issue either. Similarly, there is no obligation to monitor or regulate medicinal product residues present in sewage sludge originating from water treatment plants. This issue is however taken into account sporadically by the national legislation: the use of sludge in agriculture is for instance restricted in Bavaria and *Nordrhein-Westphalia* to take into account the environmental risks posed by the presence of pharmaceutical residues.

As for the aquatic compartment, the Commission proposed (in 2012) the inclusion of three active pharmaceutical ingredients (E2, EE2 and Diclofenac) in the list of priority substances under the Water Framework Directive. The Commission also proposed a watch-list mechanism for gathering monitoring data to support future reviews of the list. The adopted compromise text places the three active pharmaceutical ingredients on the first watch list. Member States will be obliged to monitor substances on the watch list at least annually at a limited number of representative monitoring stations for up to four years. Member States may also identify and monitor medicinal products as specific pollutants pursuant to existing provisions of the Water Framework Directive (Annex VIII).

EU food legislation requires the monitoring of veterinary medicinal products residues in foodstuffs of animal origin, but does not refer to medicinal products for human use. As a consequence, EU food legislation does not address the issue of indirect transfer to humans of residues of medicinal products for human use, which may be present and have accumulated in the natural environment and may be transferred to food animals including fish. However, further studies would be needed to fully characterise this possible exposure pathway in order to evaluate its significance.

Non-legislative factors

One of the major factors is the overconsumption of medicinal products, which can occur at the time of purchase and/or during the administration of a medicine. Although the use of medicinal products to meet needs for medication is hardly questionable, inappropriate and excessive consumption might be at the origin of unnecessary emissions. The concept of "overconsumption", i.e. consumption beyond actual needs, is an easy grasp but it is difficult to assess the scale of this phenomenon in practice, given the subjectivity of what is "needed". Through consultations and prescriptions, doctors are competent for assessing these needs for each patient. However, in practice, the OTC status and a number of medical habits and socio-economic factors might favour the overconsumption of medicinal products.

Regarding the strategies for administering medicinal products, the non-optimal targeting of symptoms (i.e. non optimally targeting the localisation of pain/injury) can increase the amount of APIs administered.

As for waste management, when a separate waste stream for medicinal products exists, the low performance of collecting unused medicinal products (as reported in some MS) and the heterogeinity in EU take back schemes efficiency is a key factor and could be further considered. Moreover, most current urban wastewater treatment plants cannot guarantee complete elimination of excreted medicinal products.

What are the major uncertainties?

The issues presented in the previous sections, in particular the scale of the problem, environmental behaviour and impacts, are subject to uncertainties as the research in this field has been limited to some specific medicinal products and is difficult to generalise. These uncertainties are related to availability of data concerning the quantity and nature of medicinal products reaching the environment from the different stages of the life cycle, their behaviour in the environment, the full characterisation of possible exposure routes for humans and thus to the scientific knowledge necessary for a proper risk evaluation.

Regarding the characterisation of the life cycle, it is worth noticing that the available data on EU consumption is relatively scattered. Also, sales data is often confidential and it is particularly difficult to obtain data on medicinal products sold over the counter (OTC) or via the internet. Similarly, detailed knowledge regarding the fate of uncollected unused medicinal products, and regarding other practices, notably concerning the administration and the collection of unused veterinary products, is currently missing.

A large amount of information is now available, notably concerning the monitoring of certain active substances insurface and groundwater used for the production of drinking water, , but the available data are not centralised and not in a standardised format. Environmental concentrations are scarce or missing for some environmental compartments, notably for biota in the food web and marine ecosystems. Information is scarce on the environmental occurrence and fate of metabolites and transformation products due to knowledge gaps in their behaviour in the environment, and/or detection issues.

The information regarding the environmental impacts is not sufficient for the majority of medicinal products currently on the European market, in part because of the insufficient publically available data on the ecotoxicology of many pharmaceuticals, and often deduced from few acute ecotoxicity data collected from a very limited number of freshwater species. It should also be pointed out that the knowledge on environmental occurrence is equally limited for many pharmaceuticals, making a sound and transparent environmental risk assessment almost impossible in many cases. In order to gain a better understanding of the environmental hazards of pharmaceuticals, their ecotoxicologically relevant modes of action need to be better identified and clearly differentiated from the modes of action that are relevant in a human pharmacological and toxicological context (although, of course, there might be overlaps for certain groups of compounds). In particular, possible effects in an ecological context, i.e. on a super-organism level, warrant more attention.

The environmental exposure of humans to medicinal product residues is a fact, and occurs through several pathways. However, the information on exposure through the environment is very sparse with the exception of certain residues which have often been detected at very low levels which are without concern for humans, as far as can be determined on the basis of current knowledge. Most

of these exposure pathways are probably not very important but some pathways, such as dairy products, still need to be fully characterised and long-term effects cannot be ruled out especially with regard to more vulnerable populations. In addition to this uncertainty, there is growing concern that combined exposure to chemical mixtures, including medicinal products from different sources, may have adverse effects on human health, even if each individual substance is below its own risk limit, and experts regard the predominant chemical-by-chemical approach currently used in risk assessment as insufficient to protect against the risks of combination effects.

What are the possible solutions to mitigate the issue and reduce uncertainties?

To tackle the issues highlighted in the report, a number of possible solutions have been identified, both legislative and non-legislative. However, no impact assessment of these options is made, as this is beyond the scope of this study. The effectiveness of the proposed solutions to cope with the environmental impact of medicinal products would need to be further assessed, in light of their impacts on the use of medicinal products and the protection of public health.

The key steps of legislative actions concern – but are not limited to – the strengthening of the ERA in the framework of MA. Major non-legislative solutions focus on consumption and waste management steps of the life cycle. The proposed solutions may help in reducing the uncertainties and to mitigate the issue, but will need a detailed evaluation in order to assess their relative weight and develop an action plan giving priority to the most appropriate ones.

Legislative solutions

Based on our preliminary analysis of solutions, the ERA framework could benefit from a change in scope, notably by focusing on APIs rather than final products. This will allow for an evaluation of the real burden of active substances present in the environment, often coming from different medicinal products. In the case in which excipients present hazardous characteristics, consideration of the full product could be considered as well. The action limit and endpoint could be updated, taking into account metabolites at early stages and requiring a PBT assessment for all pharmaceuticals, which would need to be more consistent with other frameworks of internationally recognised PBT evaluation frameworks. The results of the ERA assessment of APIs could then be fed into a monograph system similar to what already exists under REACH and the biocides and plant protection products legislation, leading to a dedicated centralised internet database. This will help in improving the availability and the comparability of results. ERA data for human medicinal products could then be considered for the risk/benefit analysis, thus having a more important role in the MA process. Finally, the implementation and the efficiency of existing RMMs could be verified and ameliorated when necessary.

The ERA procedure could also equally target «old» pharmaceuticals through a «catching-up» procedure. This could be done after a prioritisation of substances to assess their potential environmental risks. If the process of ERA will be modified, the associated guidelines could of course be reviewed in line with the modifications.

It could also be considered to amend EU medicines legislation so that monitoring data (particularly for water, obtained pursuant to the Water Framework Directive) could be used for post-market evaluation of authorisations, which could lead to possible revision of RMM or even MA withdrawal. The Water Framework Directive could also serve to facilitate the explicit consideration of ERA results for active pharmaceutical ingredients in the assessment of substances to be added to the priority substances list or watch list. It could be used to include provisions requiring Member States to make publicly available and easily accessible (e.g. through a dedicated database such as the European Pollutant Release and Transfer Register) water monitoring data regarding substances listed in the priority substances list and watch list regarding pharmaceutical substances. Water monitoring data for priority substances and substances on the watch list communicated by water authorities could then also be taken into account during the evaluation of MA applications and for post-reassessment of MA.

Tailored legislative tools could also be implemented to limit emissions in the environment by establishing a specific label for green pharmacy, by imposing more stringent requirements for emissions "hot spots", and reminding national competent authorities of the need to classify pharmaceutical wastes as hazardous waste, when appropriate, under entry 07 05 13* (solid wastes containing dangerous substances).

Non-legislative solutions

In addition to the legislative solution proposed above, a number of non-legislative actions have been initially identified as a possible support in the mitigation of medicinal products presence in the environment, through the establishment of an EU eco-pharmacovigilance framework. Some of these non-legislative actions are directly linked to the revision of the ERA framework and would help its implementation, for instance by encouraging the recruitment of personnel with an eco-toxicology background in regulatory agencies or developing European guidelines for the implementation of harmonised approaches for the environmental classification of medicinal products in MS. In parallel, training sections could be organised for medical doctors in order to increase awareness on the various environmental issues related to prescription strategies. The adequacy of packaging sizes to consumers' needs and doctor's prescriptions might be reconsidered and there could be a need for systematic reporting of internet and OTC sales. Take-back schemes for unused medicinal products represent one of the simplest way to reduce inputs of pharmaceutical products into the environment Major improvements in waste management could then be focused on the improvement of collection schemes for unused human and veterinary medicines, as well as on tracking their efficiency. Finally, more efforts are needed to improve and harmonise monitoring and prioritisation strategies. Research initiatives could then focus on prioritising medicinal products based on publicly available, high quality data on chronic ecotoxicity, which are still scarce or even absent for a broad range of human and veterinary medicinal products. Knowledge on the ecotoxicity of medicinal products to terrestrial and marine organisms is even more limited. The development of methods to assess ecological and health effects of medicinal products, notably due to chronic exposure at low doses, and to mixtures of chemicals, will help complement the current guidance on how to perform the risk assessment for humans and the environment.

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Chapter 1: Introduction

A **pharmaceutical medicinal product**, also referred to as a **medicine** or **medication**, can be generally defined as any chemical substance - or product comprising such - intended for use in the medical diagnosis, cure, treatment, or prevention of disease. Three thousands active pharmaceutical ingredients (APIs) are currently authorised on the EU market (Touraud, 2011), amongst about 4000 worldwide, with an overall consumption of about 100 000 tons or more every year (KNAPPE, 2008).

Medicinal products[1] are, by their very nature, biologically highly active and they are consumed in high amounts, which might pose an issue in terms of quantity and quality of emissions during their life cycle. The presence of medicinal products in the environment is a globally emerging issue (Boxall, 2012) (Larsson, 2007) (Babic, 2007) (Li, 2008a&2008b) (Cui, 2006) (Bisarya, 1993). Medicinal products residues of various categories (hormones, anti-cancer, antidepressants, antibiotics, etc.) have been detected in all environmental compartments, such as surface water, groundwater, soil, air, biota and in wastewater (sewage), (Heberer, 2002) (Kümmerer, 2009) (Halling-Sørensen, 1998) (Touraud, 2011) (Kümmerer, 2008) (Williams, 2005) (Ternes, 2001) (Buerge, 2006) at concentrations ranging from sub-ng/L levels to µg/L. Such widespread occurrence obviously begs the question whether these concentrations of medicinal products in the environment might pose a risk for the exposed biota or humans.

Recent pharmacovigilance legislation in the EU acknowledges that the pollution of waters and soils with pharmaceutical residues is an emerging environmental issue3. The European Commission was asked to deliver a report on the scale of the issue, the causes, and possible policy options to mitigate such impacts. More recently, in the framework of the adoption of the Directive regarding priority substances in the field of water policy, the Commission has been asked to develop, instead of the report, a strategic approach to pollution of water by pharmaceutical substances by the end of 2015. This study, contracted by the EAHC to BIO Intelligence Service is intended to support the Commission in producing the report.

1.1 Objectives

The main goals of the study are to:

- Provide an assessment of the scale and trends of the emerging issue related to the presence of medicinal products (human and veterinary)[2] in the environment and their possible impacts;
- Analyse the legislative and non-legislative factors possibly influencing the issue, i.e. if and eventually how efficiently the environmental and health issues related to the

[1] Including the active pharmaceutical ingredient, as well as adjuvant substances, metabolites and transformation products

[2] Personal care products are not in the scope of the study

presence of medicinal products in the environment are tackled by the current legislation and current practices; and

- Identify policy options to improve the current framework and discuss their feasibility.

1.2 Report structure

In addition to this introductory chapter, the report is structured in eight chapters. The chapters 2 to 6 provide a picture of the scale of the issue of the presence of medicinal products in the environment; the causes are presented in Chapters 7 and 8, while potential solutions are discussed in Chapter 9. A brief description of each chapter is presented below.

- **Chapter 2: Medicinal products – A life cycle perspective**

  It provides key facts and figures on medicinal products life cycle.

- **Chapter 3: How do medicinal products enter the environment?**

  This chapter presents the scale of the issues in terms of quality and quantity of active substances entering into the environment, following different pathways, from cradle to grave.

- **Chapter 4: Which molecules are found in the environment and how do they behave?**

  This chapter describes that once in the environment, medicinal products are not homogenously distributed. It also explains how the behaviour of these products depends upon the environmental compartment and the medicinal molecule.

- **Chapter 5: Environmental hazards**

  This chapter identifies the potential impacts of the release of medicinal products on the environment.

- **Chapter 6: Human exposure through the environment and possible impacts**

  This chapter analyses the impacts on human health through environmental exposure.

- **Chapter 7 and Chapter 8: Factors of influence**

  The presence of medicinal products in the environment can be influenced by a number of factors: - legislative, technical, administrative, etc. These are discussed in this chapter and illustrated through seven case studies. The cases studies in detail are presented in the annexes.

- **Chapter 9: Possible solutions**

  This chapter focuses on possible solutions, which could be of legislative or non-legislative nature, and might target different causes, stakeholders, life-cycle steps, etc.

- **ANNEX 1: Usage of medicinal products in aquaculture – cases of Norway and the UK**

  This annex describes aquaculture practices.

- **ANNEX 2: Examples of monitoring data in the environment**

This annex presents some results of monitoring in different environmental compartment and EU countries.

- **ANNEX 3: case studies on specific medicinal products**

  This annex presents 8 case studies of pharmaceuticals, discussing the current scientific knowledge and the specificities of the procedure for the market authorisation.

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Chapter 2: Medicinal products – A life cycle perspective

This chapter presents key definitions and background information on the life cycle of medicinal products, which are essential for understanding their environmental implications.

2.1 Key definitions

This report uses "medicinal products" as the generic term for "pharmaceuticals" or "drugs" which are administered to human and/or animals. The Directive 2001/83/EC[3] defines human medicinal products as:

"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."

Similarly, the Directive 2001/82/EC[4] provides a definition of veterinary medicinal products:

"Any substance or combination of substances presented for treating or preventing disease in animals, or any substance or combination of substances which may be administered to animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in animals is likewise considered a veterinary medicinal product."

Following are some other important definitions used in this report:

- **Active Pharmaceutical Ingredients** (API) are the substances in medicinal products which are pharmaceutically active.
- **Metabolites** are the products resulting from structural changes that medicinal products may undergo within the body or on the skin of humans and animals. Metabolites may be formed by biological and/or non-biological processes. They may also result from the activity of metabolic pathways of humans and treated animals, as well as from changes performed by other organisms living within or on the body of humans and treated animals, and from non-biotic processes occurring there (Kümmerer, 2009).

[3] Directive 2001/83/EC of The European Parliament And of The Council of 6 November 2001 on the Community code relating to pharmaceuticals for human use
[4] Directive 2001/82/EC of The European Parliament And of The Council of 6 November 2001 on the Community code relating to veterinary pharmaceuticals

- **Transformation products** are additional molecules formed after the excretion of parent compounds and metabolites in the environment.
- **Pro-drug**[5] is a medication that is administered as an inactive (or less than fully active) chemical derivative that is subsequently converted to an active pharmacological agent in the body, often through normal metabolic processes. A prodrug serves as a type of *precursor* to the intended medicinal products.

2.2 Overview of the life-cycle of medicinal products

The basic life cycle of a medicinal product consists of several stages as illustrated in Figure 1.

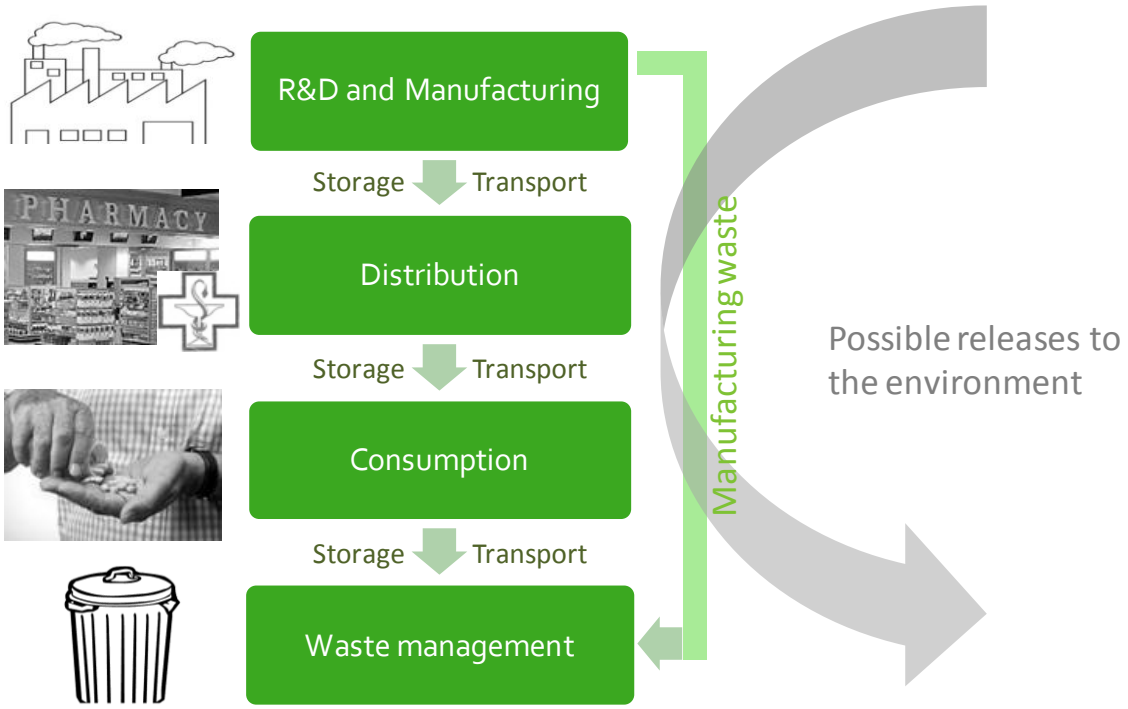


Figure 1: Life-cycle steps

These stages, which apply to both human and veterinary medicines are explicated below.

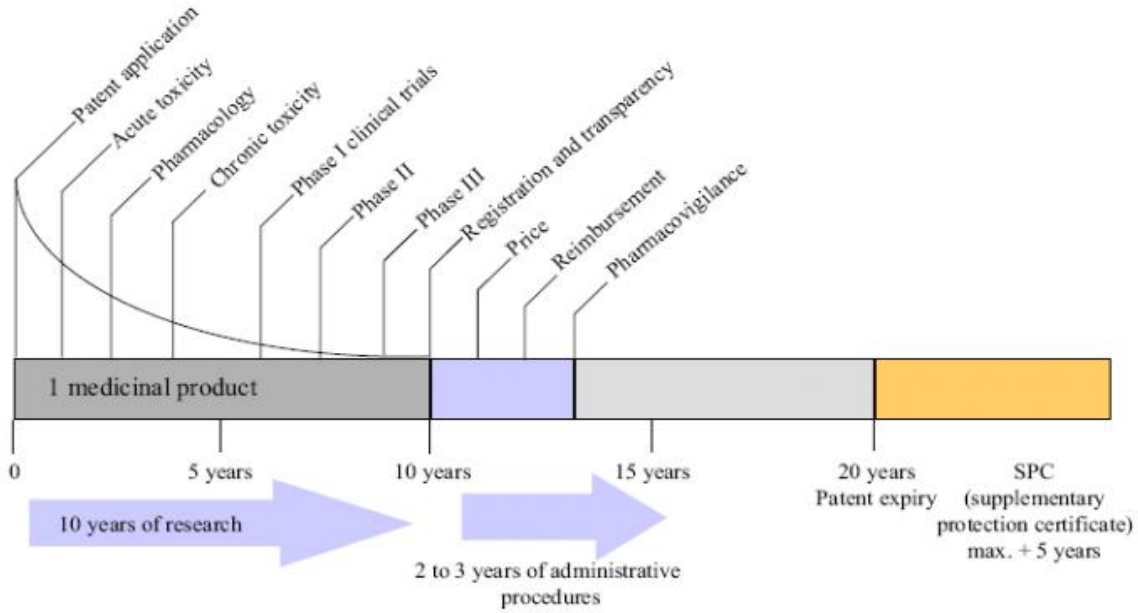
2.3 Production

The production of medicinal products can be divided into three sub-stages:

1. Research and development (R&D) of Active Pharmaceutical Ingredients (API);
2. Synthesis of the APIs, from organic and natural substances: this stage may combine several processes using technologies of high added value such as fermentation, extraction, chemical synthesis, etc.; and
3. Formulation of the final medicinal product: mixing of APIs with excipients to produce various dosage forms (such as tablets, pastilles, spray, syrup, or patch) and tastes.

[5] Pro-drug could be explained either under "active ingredient" or "metabolite"

The biological and pharmaceutical functions and properties of the molecules are explored and determined at the R&D stage. On average, only one or two of every 10 000 substances initially developed would successfully pass all the stages to become marketable medicinal products (EFPIA, 2012). The development of new molecules includes preclinical studies (proof of pharmacological activity and toxicity studies in animals) and clinical studies (tolerance and toxicity studies in several healthy volunteers, efficacy studies among several tens of patients and finally benefits/risk balance studies among several hundreds of patients). Developing a new medicine takes some 12 to 14 years on average (EFPIA, 2012) (Figure 2).



Source: World Health Organisation, 2006, The pharmaceutical industry in Europe, key data, PowerPoint

Figure 2: Route from discovery to consumer access[6]

R&D is mostly performed in developed countries, such as the United States, Japan, Germany, Switzerland, UK, France, and Sweden. Yet, the Asia-Pacific region has recently increased its R&D activities, especially in generics[7]. Whereas R&D is mostly performed in developed countries, most APIs manufacturing takes place in emerging countries, predominantly in Central and South America as well as in the Asia-Pacific region, which is set to become the global API production hub (Weinmann, 2005). This is where most of the pollution related to the manufacture of active molecules will occur.

2.4 Consumption

Human and veterinary medicinal products are consumed for preventive, diagnostic, nutritional and/or treatment purposes. Of 4 000 APIs available in the world (KNAPPE, 2008), 3 000 are currently authorised on the EU market (Touraud, 2011). However, according to the variety of pharmaceutical authorisation procedures at national level, the available estimations show that

[6] Implications of Regulation - Final report. Available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/vol_1_welfare_implications_of_regulation_en.pdf

[7] Generic: Drug product that is comparable to brand /reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics

the number of APIs varies in different MS. For example, only 850 APIs are authorised in the Netherlands (Derksen, 2004) while 2 000 APIs are authorised in the UK (Ashton, 2010), 2 684 in Germany (Pfluger, 2011) and 3 000 in France (ANSM, 2012).

2.4.1 Consumption of human medicinal products

Medicines consumption varies greatly between countries but leads to an average of 15 grams of APIs per capita per year at global level. The annual worldwide consumption of APIs is estimated at 100 000 tonnes at least (KNAPPE, 2008). Regarding human medicinal products, EU consumption of medicine accounts for 24% of the world total, ranked second after the United States (55%), the third place occupied by Japan (14%) (Académie Nationale de Pharmacie, 2008). Consumption of human medicinal products in EU is heterogeneous and varies between 50 and 150 g APIs/capita/year. France and Germany share equally about two-thirds of this consumption although the German population is 25% higher than the French (80 millions inhabitants versus 65 millions); followed by the UK, Italy and Spain (about one-seventh each) (KNAPPE, 2008) although English and Italian population are similar (about 60 millions inhabitants) but more important than the Spanish one (45 millions inhabitants). France has the highest per capita consumption of human medicinal products, followed by Germany, Spain, UK, and Italy.

Efforts have been made in the recent past to produce datasets comparing the consumption of human medicinal products consumption by active molecule in different countries, such as the 2008 KNAPPE project (KNAPPE, 2008) covering France, Germany, Poland, Spain and the UK, or the European Surveillance of Antimicrobial Consumption (ESAC) project[8] covering antibiotics consumption throughout the EU. The latter publishes the volumes of antibiotic use in ambulatory care settings, expressed in Defined Daily Dose (DDD) per 1000 inhabitants per day for the years 2003 up to 2010, for each Member State. The following table (Table 1) presents a compilation of data from various sources on the consumption of various medicinal products for humans following the therapeutic class and the MS.

Several scientific publications (Coetsier, 2009) (Le Pen, 2007) (Sabban, 2007) and official reports (Clerc, 2006) have estimated total European consumption of human medicine between 750 and 1 500 standard units[9]/capita/year (SU/capita/year), detailing each medicinal product category's consumption per Member State. For example, anti-hypertension medicinal products and analgesics are the most consumed (about 500 SU/capita/year each), followed by psychoactive medicinal products (300 SU), anti-cholesterol or diabetes medicinal products (about 150 SU) and finally antibiotics (80 SU). France is the Member State with the highest consumption of all these categories of human medicinal products, except hypertension medicinal products for which the UK has the highest consumption.

[8] ESAC project: app.esac.ua.ac.be/public/ and ESAC database : www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50039

[9] The standard unit (SU) corresponds to the smallest common dose of a medicine, for all dosage forms (for example 1 pill, 1 tablet, 1 dose-measuring spoon, etc.). The consumption assessment in units (i.e number of box) leads to an overestimation of French consumption regarding other European countries; since packaging are different following EU states (more pill per box in Germany or UK for example).

Table 1: Consumption data of various classes of human medicinal products

Therapeutic class of human medicinal products		Number of standard units[9]/capita/year (in 2006) (Coetsier, 2009)					DDD[10] / 1000 inhabitants / day (year of data)															
		DE	ES	IT	UK	FR	EL	FR	PT	SK	IT	BE	PL	ES	FI	SI	NO	UK	SE	DE	DK	AT	NL
Non narcotic antipyretic analgesics (Lasinskas, 2009)		50	76	23	117	146									100 (2007)		80 (2007)				124 (2007)		
Anti-hypertension medicinal products	all	144	82	108	118	110																	
	β-blockers	39	12	17	24	23																	
	IEC and sartans	51	36	49	34	39																	
Psychoactive medicinal products	Antidepressant (OECD, 2011a)	17	21	14	28	29		50 (2003)	72 (2003)	27 (2003)		67 (2003)		58 (2003)	66 (2003)	43 (2003)	55 (2003)	61 (2003)	74 (2003)	42 (2003)	78 (2003)		40 (2003)
	Sedative	5	36	22	6	40																	
	Anti-epileptic	11	15	10	17	13																	
Anti-asthmatic		56	70	18	175	78																	
Anti-cholesterol medicinal products (OECD, 2011a)		21	23	18	32	42		92 (2003)	90 (2003)	97 (2003)		110 (2003)		74 (2003)	91 (2003)	74 (2003)	104 (2003)	121 (2003)	71 (2003)	62 (2003)	99 (2003)		89 (2003)
Anti-diabetes medicinal products (OECD, 2011a)		25	30	28	28	36		66 (2003)	69 (2003)	50 (2003)		55 (2003)		62 (2003)	80 (2003)	54 (2003)	47 (2003)	70 (2003)	50 (2003)	79 (2003)	44 (2003)		66 (2003)
Antibiotics (ESAC, 2006)		8	18	14	19	22	32 (2003)	28 (2003)	27 (2003)	27 (2003)	26 (2003)	24 (2003)	21 (2003)	20 (2003)	19 (2003)	17 (2003)	16 (2003)	15 (2003)	15 (2003)	14 (2003)	14 (2003)	13 (2003)	10 (2003)
Anti-ulcerous medicinal products		12	29	16	19	22																	

[10] Defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults

The consumption of medicinal products (i.e. consumed volumes) varies considerably from one country to another (Verbrugh, 2003) (Goossens, 2005) (Schuster, 2008) (Ministère de l'Ecologie, 2010), although these numbers should be interpreted with care as the quality of reporting varies across different sources. For instance, analgesics are consumed at a total rate of more than 2 600 tonnes/year in the EU (Bergmann, 2011). However, the French ingest 47 grams of Paracetamol each year (60% of analgesics sold molecules)/capita (KNAPPE, 2008) instead of 16 grams for English people or even 4 grams for Italian or German people (Sadezky, 2008). Another example is antibiotics consumption in ambulatory care, i.e. outside the hospital, which is also extremely heterogeneous in the EU: countries in the South and East of Europe have the highest consumption, whereas consumption is much lower in the Northern countries (ESAC, 2006). For example, the French consume about 30 daily doses of antibiotics/1 000 inhabitants/day compared to only 10 for the Netherlands; or 6.5 g/capita/year of amoxicillin (antibiotic best-seller in France) compared to 1.2-1.4 g/capita/year in Germany or the UK(GACE, 2007). Consumption trends (increase, decrease or stable) can also vary considerably from one class of medicinal products to another. An overall decrease in antibiotic use was observed in Europe in 2011, especially in Estonia, Slovenia, Portugal, France, Hungary, and Slovakia, whereas EU consumption of anti-diabetic products increased by 75% between 2000 and 2009 (OECD, 2011b). There are even more drastic differences, e.g. in consumption of slimming preparations (which have much more problematic properties than Paracetamol from ERA point of view).

In addition to studies focusing on the main APIs - as opposed to whole medicinal products - consumption at Member State level (MEDICAM, 2007), the KNAPPE project (KNAPPE, 2008) provides a comprehensive overview at EU level for veterinary and human APIs. It reports annual consumption levels exceeding 50 tonnes/year like the analgesic Paracetamol and Diclofenac, the antibiotic Sulphamethoxazole or Amoxicillin, the anti-epileptic Carbamazepine or Valproic acid and the psychoactive Lorazepam, as well as the anti-diabetic Metformine or the antihypertensive Metoprolol (GACE, 2007). However, the information is more scattered for other molecules, and it is even more difficult to have data on medicinal products sold over the counter (OTC) or via Internet[11].

The common use of human medicinal products can be totally disrupted in case of epidemic or pandemic situation. Indeed, the medicinal treatment of humans in epidemic/pandemic situations has similar character with mass-treatment in veterinary medicine.

2.4.2 Consumption of veterinary medicinal products

Veterinary medicinal products are used in smaller quantities than human medicinal products. Veterinary medicinal products are extensively used in farming for therapeutic and metaphylactic purposes (which represent more than 95% of the use of medicines in the rearing of piglets and turkey, more than 70% of the use of medicines for pigs and poultry and 30% of the use of medicines for bovine) (Kools, 2008). Some commonly used treatment practices, such as campaign treatment of all animals in the farm, need very high quantities of veterinary medicinal

[11] For example, the consumption data from Germany, Poland, Spain and the UK (England and Wales) do not include OTC-drugs, although detailed data exist for France (KNAPPE, 2008).

products. For example, if 1 000 cows or 10 000 pigs or 100 000 poultry are treated through feed, the quantities of the used preparation of veterinary medicinal products in the campaign may be remarkably high. The types of medicinal products used and prescribing patterns (dosage, length of treatment periods and formulation) may vary significantly for the various species in different countries, as for antimicrobials (EMA, 2010). In Germany for instance, 98 % of the antibiotic APIs in veterinary medicines are used for treating pigs and poultry, while the remaining 2 % are spread among other species (GACE, 2007). In Belgium on the other hand, cattle farming is a major consumer of antimicrobials. There is no overall EU picture regarding these figures.

The quantities of veterinary medicines consumed in the EU are also significant. In 2009, approximately 2300 tonnes/year of veterinary APIs were sold in CZ, DK, FI, FR, NL, NO, SE and the UK, although decreasing trends for the sales of antimicrobials were recently observed in these countries (- 8.2% mg/PCU[12] from 2005 to 2009)[13,14] (Figure 3). This decrease was mainly due to a decrease in the sales of tetracyclines.

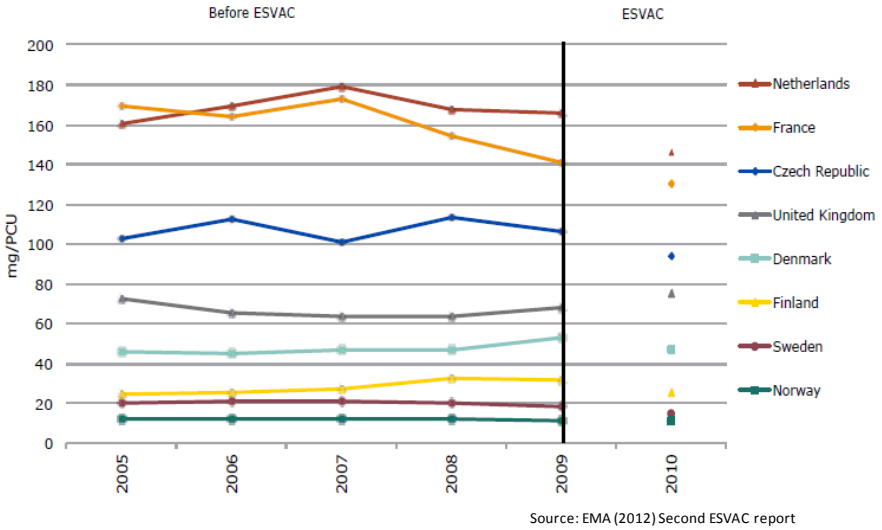


Figure 3: Sales of veterinary antimicrobial agents (expressed in mg per population correction unit (mg/PCU))[15]

It is possible to deduce the consumption quantities from MS statistics (for example, in Germany in 2006 the veterinary medicine consumption was about 700 tonnes/year (GACE, 2007), accounting for 10% of the total consumption of medicinal products which exceeded 7 000 tons/year. Some competent authorities provide detailed statistical analysis (available for instance for Denmark[16] and France[17]. Quantitative data on consumption could also be gathered from

[12] PCU: mg active substance per 'population correction unit, i.e.per estimated kg live-weight of the populations of food producing animals.
[13] In particular, the subclasses of tetracyclines (for their efficient, low cost and wide spectrum (Académie nationale de Pharmacie, 2008)), sulfonamides and macrolides (KNAPPE, 2008).
[14] Detailed information on the sales in the eight countries is available from the national reports in Annex 4 of (EMA, 2012), Second ESVAC report.
[15] Data for number of slaughter pigs were updated for the PCU for Norway for 2005-2009, due to errors in the original data. Sales data for 2005-2009 were obtained before the ESVAC protocol and harmonised collection of data were implemented. Data for 2010 should not be used to evaluate development in the sales from 2009 to 2010.
[16] Available at : www.ssi.dk/Sundhedsdataogit/Dataformidling/Laegemiddelstatistikker.aspx

[17] For instance, in Chevance, 2008.

scientific publications[18]. For example, in 2006 in France, the amount of antibiotics sold for veterinary purposes (Tetracycline essentially) was much higher than in other EU countries, and would be equivalent to the amounts sold for human consumption, which is in general not the case for other countries (Chevance, 2008). Indeed, about 1 190 tonnes/year of APIs (of antibiotic veterinary medicinal products) were used in France in 2006 versus 670 tonnes/year for Germany and Spain, about 400 tonnes/year for UK (Veterinary Medecine Directorate, 2011), Italy, Netherlands and Poland, and less than 100 tonnes/year for the others) (GACE, 2007).

Since 2010, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project also collects information across the European Union (EU), but specifically on antimicrobial medicines. Data for 2010 (EMA, 2010) show the heterogeneity in veterinary medicinal products consumption among MS (excluding Germany), with an apparent 30-fold difference in sales of antimicrobials (antibiotics are part of the antimicrobial therapeutic class), in mg/PCU, between the most and least-selling countries (EMA, 2012) (Figure 4).

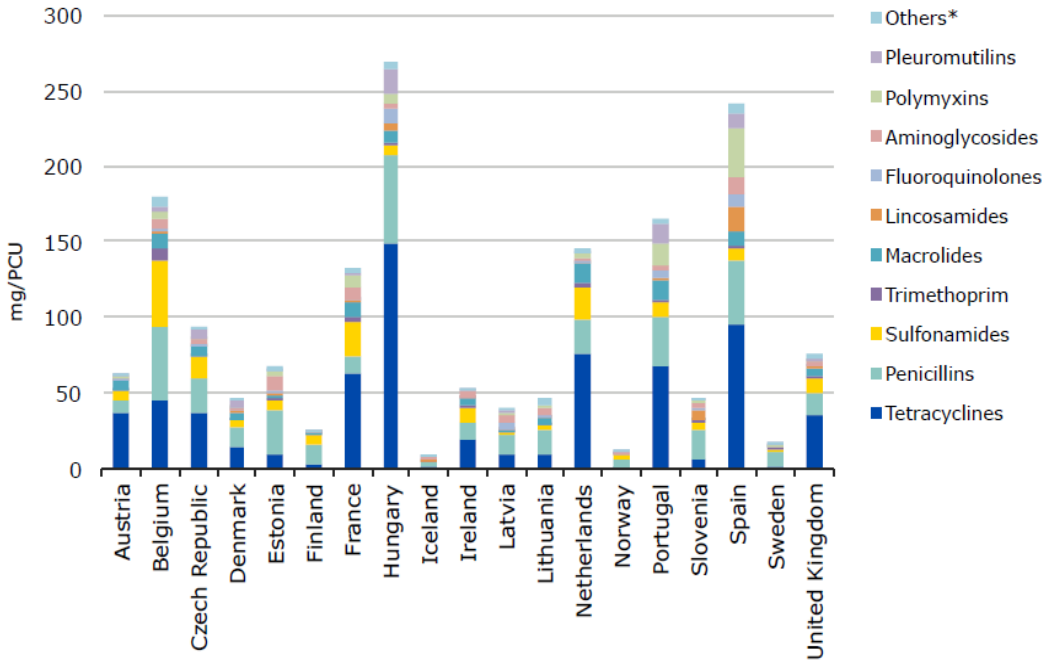


Figure 4 : Sales for food-producing species, including horses, of the various veterinary antimicrobial classes for 2010 (in mg/PCU, by country) (EMA, 2012)

Others: cephalosporins, other quinolones and other antibacterials (classified as such in the ATC vet system).

In 2010, Spain and France had the highest total antimicrobial sales for food-producing animals (respectively 1746 tonnes and 997 tonnes), but the Figure 4 shows that, when considering the animal population of each country, Hungary and Spain had the highest antimicrobial sales per food-producing animal (respectively 268 mg/PCU and 241 mg/PCU). Overall, in the 19 MS, tetracyclines, penicillins and sulfonamides were the most-sold antimicrobial classes, accounting for 39%, 23% and 11% of the total sales in mg/PCU, respectively. Data are also available for

[18] For example, Dutch figures for veterinary medicinal products can be found on the website of research institutes such as www.maran.wur.nl/UK/ (funded by industry and government).

another veterinary products class, parasiticides and non-steroidal anti-phlogistics[19] with a consumption of 28 tonnes/year in France or Spain, and less than 10 tonnes/year in the other MS.

In general, the range of molecules available for human medication is much broader than the range of molecules used for veterinary purposes. For instance, in Germany, about 2% only of all types of medicinal products sold could be intended for use in animals (EMA, 2012).

A growing segment of the veterinary products market is the companion animals, or pets – in contrast with farming animals one. The 4% growth observed for the global market of veterinary products between 2002 and 2008 was mainly due to the pets' medicinal products market growth (+8% alone). In 2011, the companion animals segment stands for 38% of the global veterinary sales[20] (only in France, almost 11 million cats (1st rank in Europe) and 7.7 million dogs (2nd rank in Europe) are registered).

Antibiotics account for a large part of the veterinary market. In France, large-scale animal farming uses 1 180 tonnes/year of antibiotics compared to 28 tonnes/year of parasiticides and 0.7 tonnes/year of hormones. Antibacterial substances are also utilised in aquaculture production with the purpose of prevention (prophylactic) and treatment (therapeutic use) of bacterial diseases (Lupin, 2003). The compounds utilised in aquaculture are of the same type utilised to treat bacterial diseases in humans. In Europe, only 14 medicinal products are authorised and approved for aquaculture (Rodgers, 2009), including seven antimicrobial/antibiotic medicinal products, six microbiocides/ antiparasitic medicinal compounds and one anaesthetic. Annex 1 presents the dosage and quantities of medicinal products used in salmon aquaculture.

The antiparasitic medicinal products represent the most important part of the market. Only 1-2% of the veterinary antibiotics sold are for companion animal only, as the large majority is for farming animals (93%) (Chevance, 2008). About 5 to 7% of veterinary antibiotics can be used for either companion or farming animals. For example, pets dedicated sales represent 0.07% of French tetracyclines annual sales (0.05 tons), 4.7% of beta-lactamines sales (5.3 tons), 1.5% of sulfamides sales (3.2 tons) and 1.9% of macrolides sales (2 tons). Nevertheless, 63% of cephalosporin market is dedicated to pets, and 100% furans market too. Moreover, the quantity of antibiotic sales for pets is increasing in France (+31% between 2000 and 2006, from 14.6 to 19.1 tons) whereas those for farming animals is decreasing (-9% for the same period, from 1281 from 1167 tons). About 20 tons of antibiotic (tons of active substance) were sold for cats in France in 2006 and 31 tons for dogs. For comparison, among the 447 tons of veterinary antibiotics sold in the United Kingdom, 35 tons (8%) were dedicated to companion animals (cats, dogs, and horses) but only 11 tons for dogs and 2 tons for cats (Veterinary Medecine Directorate, 2011).

2.4.3 Overall market trends

Industrial production and sales in the market lead to that overall medicinal products consumption has increased in the EU over the past two decades (EFPIA, 2012). There is also an increasing trends in R&D investment. The EU medicinal products market has risen from EUR 48 billion in

[19] These active ingredients have broad effect specificity and are not metabolised by the organism, both properties with a high degree of environmental relevance.
[20] www.merci-les-medicaments-veterinaires.com/enjeux.php?id_menu=56

1990 to EUR 172 billion in 2007 and is expected to amount EUR 242 billion in 2014 (LEEM, 2011) (GlaxoSmithKline, 2009). For example, in 2006, the French spent EUR 547 for their medicinal products per capita (LEEM, 2011) compared to EUR 467 in 2002 or only EUR 95 in 1980 (Académie Nationale de Pharmacie, 2008). An annual growth of this market of +3.9% between 2008 and 2013 (ECORYS, 2007) or between +1% and +4% between 2011 and 2015 is forecasted at world level (IMS Health, 2012). However, this growth trend is slowing down in the EU. In terms of value of sales, growth in 2008 was negative (-0.4 %) for the first time in many years (IMS Health, 2012). In France, a small growth of +0.5% was observed in 2011 according to ANSM and a decline (-1%) is expected between 2011 and 2015. Indeed, future changes in demographics and lifestyles are likely to influence pharmaceutical trends, especially of some molecules: antibiotic consumption is decreasing whereas anti-diabetic medicinal products and those for cardiovascular diseases are expected to see the fastest growth (Pharmaceutical Drug Manufacturer, 2012) as the fraction of diabetic people, and so prescription of these medicinal products, is increasing in EU (Filion, 2009).

In parallel, accordingly to industrial position papers, different regions of the world will increasingly influence consumption trends by changing supply and demand patterns. A shift is notably expected in the Asia-Pacific market because of the rising income and the development of health insurance schemes.

2.5 Waste management

Medical waste includes unused medicinal products (human or veterinary) and contaminated materials (e.g. packaging) and liquids (Castensson, 2008) generated during manufacturing and administration. The excretion issue is not addressed here. It is considered as emissions resulting from the consumption stage and will be addressed in Chapter 3:, section 3.2.

Medical waste stream is very heterogeneous in terms of quantities and/or quality, which poses a significant challenge for waste storage, collection, and disposal (NRDC, 2009) (Bound, 2005). Depending on the type of waste stream, it can be discharged in landfills, incinerated, or treated in water treatment plants, with a large share of medical waste being sent for incineration (EEA, 2010).

According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), unused medicinal products destined for humans represent 3 to 8% of the medicinal products sold[21]. Other estimations from KNAPPE are more pessimistic with a proportion of medicinal products sold unused from 5% in Sweden (APOTETEK, 2006) to 50% in France (Grass, 2005) and UK (Bound, 2005). The START project assessed a global amount of 5 700 tonnes/year of unused medicinal products in Germany (START, 2006). According to the results of the KNAPPE project, the human medicinal products that predominate (in terms of the numbers of packs) among those that are left over are medicinal products for cardiovascular disease, asthma, the nervous system and the gastro-intestinal tract (KNAPPE, 2008).

[21] Presentation given by Michael Murray, representative of pharmaceutical industries, during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012.

EU medicinal legislation has required take-back schemes for unused and expired human medicinal products since 2004 (Directive 2004/27/EC) to "ensure that appropriate collection systems are in place for human medicinal products that are unused or have expired" (Article 127b). Most of the 28 countries interviewed in the EEA survey reported or estimated the amount of collected unused medicinal products between 10 and 100 tonnes/year/million capita (EEA, 2010).The collection of unused medicinal products from households is estimated to range from 0.19 tonnes/year/million capita in Croatia to 237 tonnes/year/million capita in Switzerland (Sadezky, 2008). This programme is very effective in Sweden, where 74% of the Swedish public disposed their unused medications (5% of sales) by returning them to pharmacies in 2006 (APOTETEK, 2006). Nevertheless, in the majority of EU Member States, a big share of unused medicinal products (from 50% up to 90%) are not collected or returned to pharmacies (EEA, 2010), for example, in France only 6% of medicinal products sold (10% of unused medicinal products) are returned(Académie Nationale de Pharmacie, 2008).

2.6 Chapter summary

2.6.1 Key messages

- Depending on the life-cycle stage considered, many countries worldwide are concerned by the risk of release of medicinal products in the environment, notably, most APIs manufacturing takes place in developing countries, predominantly in the Asia-Pacific region as well as in Central and South America .
- About 3000 APIs are currently authorised on the EU market as a whole, however the APIs authorised varies significantly across MS.
- Industrial production and sales in the market lead to that overall medicinal products consumption has increased in the EU over the past two decades. The EU medicinal products market has risen from EUR 48 billion in 1990 to EUR 172 billion in 2007 and is expected to amount EUR 242 billion in 2014
- In general, the molecules used in human medicinal products are much more diverse than those used in veterinary medicine (for both pets and food-producing animals). For instance, in Germany, about 2% only of all types of medicinal products sold areintended for use in animals.
- Regarding human medicinal products, EU is the second biggest consumer in the world (24%) after the United States (55%). However, human medicine consumption in the EU is heterogeneous and it varies between 50 and 150 g/capita/year across MS.
- Several scientific publications and official reports have estimated EU consumption of human medicinal products, detailing in some cases the consumption of medicinal products categories per MS. Anti-hypertension medicinal products and analgesics are the most consumed (about 500 SU/capita/year each), followed by psychoactive medicinal products (300 SU),

anti-cholesterol or diabetes medicinal products (about 150 SU) and finally antibiotics (80 SU). France is the Member State with the highest consumption of all these categories of human medicinal products, except hypertension medicinal products for which the UK has the highest consumption. However, the available data is very limited and scattered. More difficult is to have data on medicinal products sold over the counter (OTC) or via the Internet. Moreover, the quality of reporting considerably varies from a MS to another.

- The consumption of veterinary medicinal products is importantin the EU when compared to the rest of the world. Veterinary medicinal products are extensively used in farming for therapeutic and metaphylactic purposes (which represent more than 95% of the use of medicines in the rearing of piglets and turkey, more than 70% of the use of medicines for pigs and poultry and 30% of the use of medicines for bovine). The companion animals segment, which stood for 38% of the global veterinary sales in 2011, represents a significant share of the market. Market data, deduced from MS statistics, show the heterogeneity in veterinary medicinal products consumption among EU countries. For instance, about 1 190 tonnes/year of antibiotics were used in France in 2006 versus 670 tonnes/year for Germany and Spain, about 400 tonnes/year for UK, Italy, Netherlands and Poland, and less than 100 tonnes/year for the others. Quality and quantity of available data also varies among different MS making a proper comparison difficult.
- Some veterinary treatment practices, such as campaign treatment, use very significant quantities of veterinary medicinal products, and the resulting «emission» may create a «hot-spot» as contaminated manure.
- Estimations regarding unused medicinal products are very heterogeneous depending on the considered EU country and source of information. According to the EEA, in the majority of MS, a large share of unused medicinal products (50%) is not collected and some MS do not yet have implemented take-back schemes.
- The medical waste stream is very heterogeneous in terms of quantities and quality, which poses a significant challenge for waste storage, collection and disposal. Depending on the type of waste stream, it isdischarged in landfills, incinerated, or treated in water treatment plants, with a large share of medical waste being sent for incineration.

2.6.2 Knowledge gaps

- Systematic and comprehensive reporting on consumption of OTC medicinal products in general and of medicinal products sold via internet is does not exist.
- Detailed market data per API or single products is not systematically available, at least not publicly.
- There is no systematic and comprehensive reporting of veterinary medicinal products going to the waste stream .

- Systematic and comprehensive reporting of human medicinal products going to the waste stream is not done, notably regarding the unused medicinal products pathways when not collected is missing, even if the difficulty in having this information is acknowledged.
- Thre is no quantitative information on the efficiency of the existing collection schemes of unused medicinal products.

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Chapter 3: How do medicinal products enter the environment?

The original substances of medicinal products as well as their residues (including Active Pharmaceutical Ingredients, metabolites[22], transformation products) may be emitted into the environment during their life cycle (Holm, 1995) (Halling-Sørensen, 1998). Various scientific monitoring and related publications (Sadezky, 2008) (Schlüsener, 2008) suggest that such emissions occur in different parts of the world, including the EU MS.

The relative importance of the sources and contamination pathways along the life cycle of medicinal products differs depending on whether veterinary or human medicinal products are considered and whether both point sources (like pharmaceutical factories or waste treatment plants) and diffuse sources are taken into account.

Both human and veterinary medicinal products can be released from the manufacturing stage, e.g. through leakages or manufacturing waste.

After consumption, human medicinal products are generally excreted as a mixture of parent compounds and metabolites (both biological active and inactive) and emitted to the sewage system. The compounds may then be released to surface waters or enter terrestrial systems through sewage effluent and/or sludge, when used for irrigation or as a fertiliser to agricultural land (Kinney, 2006). Veterinary medicinal products are released also as parent compounds and metabolites to the environment either directly, from use in aquaculture and treatment of pasture animals, or indirectly during the land application of manure and slurry from livestock facilities (Boxall, 2003).

Disposal of unused medicines may also represent emission sources of pharmaceutical compounds to the environment (Fick, 2009).

3.1 Emissions from manufacturing

In the EU and in North America, the direct contribution from production facilities to emissions of medicinal products and/or their residues have been considered negligible so far according to the European Environment Agency, despite manufacturing facilities being known to produce substantial amounts of waste[23] (EEA, 2010). The assumption that, with the exception of accidental releases, the production of medicinal products plays a minor role in their discharge into the environment (GACE, 2007), is generally based on the high economic value of the active substances (Heberer, 2002) (Kümmerer, 2009) (EFPIA, 2012) . EFPIA estimates that only 2% of the total emissions of medicinal products to the environment occur because of pharmaceutical

[22] A metabolite is an intermediate product of the metabolisation of a medicine.
[23] In the US, the amount of waste generated per kg of active ingredient produced can range from 200 to 30 000 kg (NRDC, 2009).

production[24]. However, the empirical evidence underlying these assumptions and estimations is not explicitly illustrated or presented. Moreover, a recent study showed that the discharges of a pharmaceutical manufacture could have adverse effects on the fish living downstream of a river (Sanchez, 2011). Presently, a systematic monitoring of emissions during manufacturing at EU level is missing and thus the amount of API releases from production facilities is largely unknown (APOTETEK, 2006). Moreover, possible pollution downstream from manufacturing plants has been observed in the EU and other parts of the world while monitoring specific sites: APIs have already been monitored in some manufacturing plants' effluents in Asia (Larsson, 2007) (Li, 2008a) (notably in India) and in Europe (Main, Rhine (Sacher, 2008), Lac Leman (Bernard, 2007), Loire (Togola, 2011), Norway (Thomas, 2008)). Releases during manufacturing in non-EU countries, even if not directly linked with environmental effects on the EU territory, might be of relevance for the EU. In a globalised world EU citizens can be affected by the antimicrobial resistance developed in populations from those countries, notably in the case of antibiotics. The treatment of manufacturing emissions is discussed in section 3.3.

3.2 Emissions from consumption

Of the different steps of the life cycle, the consumption stage is the most important contributor to the emissions of medicinal products into the environment (GACE, 2007) (Schwarzenbach, 2007) (Bound, 2005). It may sometimes be difficult to attribute human or veterinary origins to the residues detected in the environment (EEA, 2010) (KNAPPE, 2008), because some medicinal products can be used in both humans and animals, according to either product usage specifications or inappropriate use[25] (e.g. products for human use specifically which end up being used for animals).

The consumption step contributes to the emission of medicinal products into the environment mainly through human and farm animal excretions[26] (GACE, 2007) (EEA, 2010) (Haya, 2000) (Hecktoen, 1995) (Boxall, 2004) which are continually released in raw sewage or soil (for animals) via urine and/or faeces[27]. Figure 5 presents a schematic diagram of the known contamination pathways related to the use phase for both human and veterinary medicinal products. Although excretion is the main pathways to the environment for both human and veterinary products, significant quantities of human or pet medicinal products dermally applied, such as gels containing anti-inflammatories, can be washed off the skin during showering/bathing.

[24] Presentation given by Michael Murray, representative of pharmaceutical industries, during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012.
[25] Some medicinal products are used for both humans and animals.
[26] Excretions are addressed here, in the consumption section, and not in the end-of-life section which focuses on the issue of medical waste and unused products.
[27] Approximately 45-62 percent of the drug ciprofloxacin is excreted in human urine, while another 15-25 percent is excreted in the faeces (NRDC, 2009).

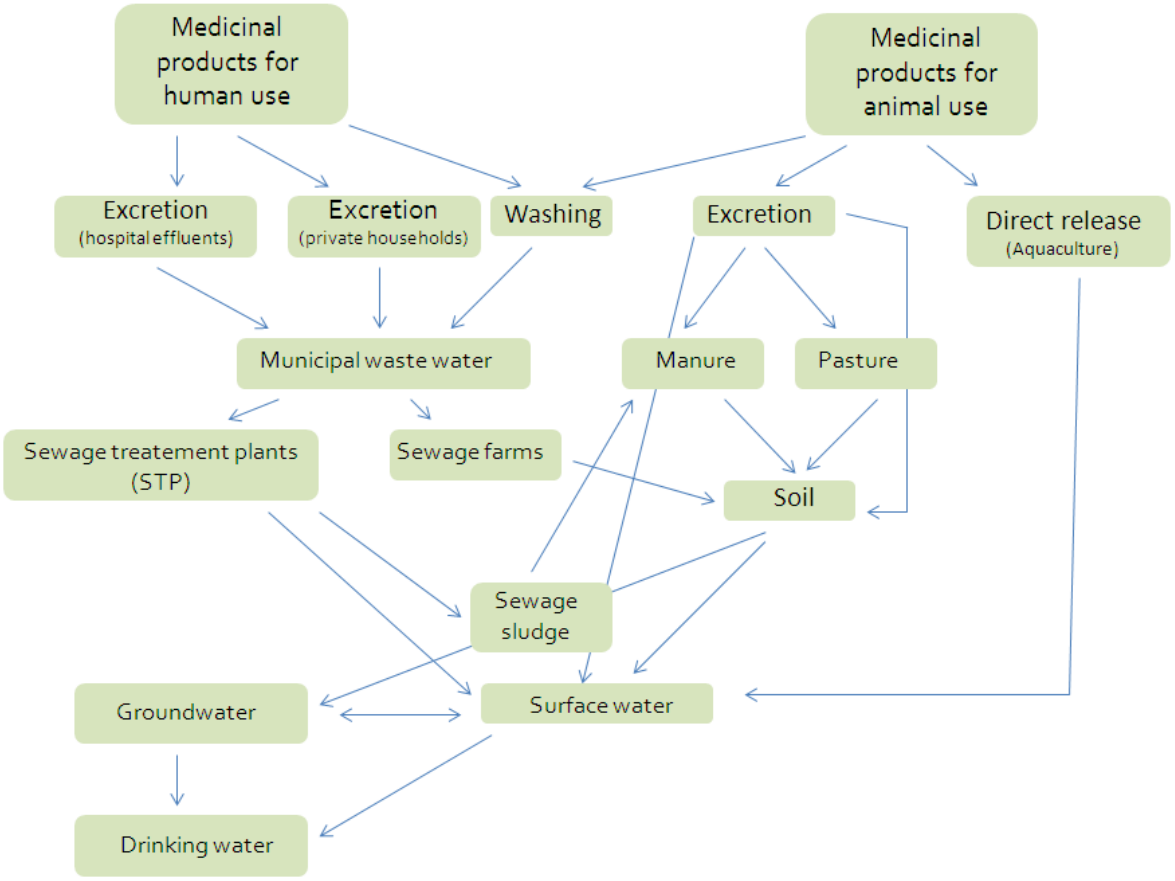

Figure 5: Emission pathways related to the use-phase of medicinal products

The nature and amount of medicinal residues released after consumption mainly depend on the volumes and nature of the administered substances, the modes of administration[28] and the metabolism rates[29] (GACE, 2007).

3.2.1 Excretions of animals and humans

Between 30 and 90% of an orally administered dose is generally excreted as an active substance (Rang, 1999) in the urine of animals (Alcock, 1999) and humans (Holtz, 2006). Significant amounts can also be excreted in faeces (up to 75% in animal faeces) (Halling-Sørensen, 1998).

- **Animal excretions**

For example, sheep excrete nearly 21% of an oral dose of Oxytetracycline, and young bulls excrete about 17–75% of Chlortetracycline (Montforts, 1999). The contribution of animal excretions to the environmental load of medicinal products has been studied (see for instance the investigation of the presence of Ivermectin[30] in dung (Lumaret, 1993; Fernadez, 2009)). This

[28] The oral route is by far the predominant administration mode, both for humans and animals (in particular through medicinal feed in large-scale breeding) (Académie nationale de Pharmacie, 2008). Other routes include parenteral route, and to a lesser extent, mammary route and external routes.
[29] In practice, the excretion rate of active substances (percentage of substance excreted once administered) may be used to calculate emissions and then the predicted concentration of pharmaceutical in the environment (e.g. done in sewers for amoxicillin, acetylsalicylic acid, diclofenac, paracetamol, atenolol, furosemide, dipyridamole, erythromycin and Ibuprofen) (Achilleos, 2005).
[30] Compounds used to reduce the impact of Lyme disease on human health by reducing tick populations in the environment.

is an important contamination pathway in the case of the re-use of organic waste, notably in agriculture, as detailed in the next section.

For the specific case of veterinary medicines for pets, there is no study quantifying the environmental emissions of medicinal products administered to pets, nor establishing the impacts of these emissions (Boxall, 2003). Nevertheless, based on dosage, pharmacokinetic data and excretion rates, it might be possible to roughly estimate the release of those compounds in the environment. For example, the veterinary medicinal products for companion animals, Medetomidine, is excreted in urine in three days (30-75% of a single dose 80µg/kg) (Salonen, 1989). Another example is pyrethrins and pyrethroids, which are used in numerous formulations (0.2-1% in shampoo, 0.8-6% in collar, 50% in solution, and 0.2-1% in aerosol) used for the control of insect pests on dog and cats. About 14-70% of an oral dose are absorbed and metabolised. Their lipophilicity triggers long elimination half-lives (about 10h) but almost all of an oral dose of pyrethroids is excreted as metabolites in the urine and faeces within a few days. However, the amount of treated animals and their mean weight would need to be known to extrapolate the amount of compound released in the environment.

- **Human excretions**

A study (Lienert, 2007) analysed the excretion pathways of 212 human active pharmaceutical ingredients (APIs), equalling 1,409 products. On average, 64% (+/-27%) of each API was excreted via human urine, and 35% (+/-26%) via human faeces. However, regarding human medicinal products, the quality and quantity of excreted molecules is highly variable. In urine, 42% (+/-28%) of each API was excreted as metabolites but there was a significant variability depending on the API. For example, 80-90% of the antibiotic Amoxicillin is released in the parent form, while only 3% of Carbamazepine is excreted unchanged (Lienert, 2007). 45-62% of Ciprofloxacin is excreted in human urine, while another 15-25% is excreted in the faeces (Golet, 2003).The excretion rates of the API EE2 or its conjugate are extremely high at 85%, the majority (50 to 90%) being excreted in conjugated form together with urine (Ranney, 1977).

Releases of excretions into the sewage system undergo wastewater treatment. This aspect is discussed in section 3.3.

3.2.2 Case of aquaculture

In most European countries, fisheries in open waters is supported by a large industry producing fish in aquaculture to provide sufficient quantity for the fish food marked. Substantial amounts of medicine can enter the environment directly (GACE, 2007) through food/feed surplus notably in aquaculture, where the breeding and keeping of commercial and ornamental fish produces direct discharges of medicinal products and feed additives into the aquatic environment, through their supply in the water (Cabello, 2006). Prophylactic use of veterinary medicinal products has been particularly developed in aquaculture, notably antibiotics, to forestall bacterial infections resulting from the high density of fishes, the difficulty in isolating sick animals and the absence of sanitary barriers (Naylor, 2005). As in other animal production sectors, antibacterial substances

are utilised in aquaculture production with the purpose of prevention (prophylactic) and treatment (therapeutic use) of bacterial diseases (Lupin, 2003). Antibacterial have been utilised as growth factors in European aquaculture for many years, even if this is an illegal practice. The compounds utilised in aquaculture are of the same type utilised to treat bacterial diseases in humans.

In Europe, only 14 medicinal products are authorised and approved for aquaculture (Rodgers, 2009), including 7 antimicrobial/antibiotic medicinal products (Amoxicillin, Florfenicol, Flumequine, Oxolinic acid, Oxytetracycline, Sarafloxacin and Sulfadiazinetrimethoprim), 6 microbiocides/ antiparasitic medicinal compounds (Azamethiphos, Bronopol, Cypermethrin, Emamectin Benzoate, hydrogen peroxide and Teflubenzuron) and one anaesthetic (Tricaine Methane Sulphonate). For example, Azamethiphos is an organophosphate insecticide (and the active ingredient in the formulation Salmosan) used in the sea lice treatment (Haya, 2000). Annex 1 presents the dosage and quantities of medicinal products used in salmon aquaculture (representing 90% of aquaculture production) in Norway and UK. Those countries are the major European producers of salmon (and among the 3 major world producers with Chile), with respectively 510 000 tons (49% of world production) and 145 000 tons (14% of world production) of salmon production in 2003 (Burridge, 2008).

Releases are particularly substantial from the breeding of shrimps and salmon. Significant emissions of medicinal products were detected in salmon and shrimps farming in Norway (Grave, 1999). Moreover, a recent survey (SEPA, 2013) measured the occurrence of medicinal products in the sediments of Scottish marine fish farms. Although the concentrations were often below the limit of detection, they measured up to 2.2 µg of Teflubenzuron / kg of dry weight sediment, 22 µg of emamectin / kg of dry weight sediment, 0.3 µg of Deltamethrin / kg of dry weight sediment, and 0.15 µg of Cypermethrin / kg of dry weight sediment.

3.2.3 Other emissions

Non-negligible quantities of human or pet medicinal products dermally applied, such as gels containing anti-inflammatories, can be washed off the skin during showering/bathing. For example, only 2% of a dermal dose of pyrethrins and pyrethroids are absorbed and metabolised (Boxall, 2003).

To a lesser extent, emissions of medicinal products can also result from their volatilisation or from the airborne transport of dust from animal sheds (GACE, 2007), although the significance of such releases into the atmosphere is still unknown (other routes, e.g. sweating, are considered negligible).

3.3 Emissions due to disposal and waste treatment

This section focuses on the emissions from the disposal of medical waste (including e.g. contaminated packaging and unused medicines) and from the treatment of sewage and solid waste, including waste streams from the manufacturing stage to the consumption stage (e.g. excretions).

Different facilities (households, hospitals, health care centres, manufacturing facilities, waste treatment plants, etc.) contribute to the occurrence of medicinal products in waste streams that need to be treated, although there is little information about their respective contributions and the available information generally covers only a part of the process or specific active substances.

In particular, hospital effluents can contribute to a variable, but non-negligible share of the medicines released in the environment through urban effluents. In the EU, hospitals contribution to medicinal products environmental load is estimated at about 10% of urban effluents (Kümmerer, 2009). However, this share can be higher, as shown for instance in Denmark, where it is estimated that 24% of the total antibiotic load in the Capital Region originates from hospitals. This figure rises to 43% if non-problematic penicillins are disregarded. For hospital-specific substances such as cytostatics, endocrine therapy or contrast media it is shown that hospitals are the overall biggest sources (70-90%) while for pain killers or blood pressure medicine they are smaller contributors[31].

3.3.1 Disposal

Medical waste (including contaminated packaging and unused medicines, from all stages of the life cycle) is usually disposed off directly in the bin (solid waste), thus joining municipal waste, in the drains (sinks or toilets) for liquids, thus joining excretions in the sewage network, or is collected through collection schemes.

Improper disposal of medicinal products has been identified as a potential major source of pollution, especially for medicines with high usage like Diclofenac, in the Impact Assessment to the proposal for revised WFD and EQSD directives (6019/12 ADD 2; dated 2 February 2012). There, it is stressed that "one 10-tablet blister of a typical 50 mg dose of diclofenac can pollute up to 5 million litres of water, with concentrations above the Environmental Quality Standards, i.e. a volume equivalent to the waste water generated daily by a town of 20 000 inhabitants". Likewise, "improper disposal of unused EE2 could be a significant source of pollution, considering that a single blister of pills for one menstrual cycle with the most common dose of 30 microgrammes has the potential to pollute to concentrations above the EQS 24 million litres of water, equivalent to the waste water generated daily by a city of 100 000 inhabitants". In the case of antibiotics, the entire discharge volume into wastewater has been estimated to be about 86 tonnes per year for European hospitals (Houeto, 2002).

Many studies have assessed the fate of unused medicinal products to determine the share discarded down the drain or toilets, out in trash or collected. An estimation concerning unused medicinal products states that on average in Europe probably 50% of the sold medicinal products are unused (EEA, 2010). In the UK, Bound and Voulvoulis showed in 2005 that about 80% of them are not collected although a more recent study however shows that only 20% of the individuals surveyed stated that they would throw away unused medicines through household waste (York Health Consortium and University of London, 2010). Amongst uncollected unused medicines, 63% would end up in the bin and 12% in sinks or toilets in the UK (Bound, 2005). In Germany, the

[31] Figures based on a comment from a representative of Denmark, in the context of the present study.

share of unused medicines being discarded into the drain would reach 23% (START, 2006). This behaviour leads to an amount of 364 tonnes of APIs flushed away every year in Germany according to START or 770 tonnes/year of unused medicinal products/year exposed in sewage (Götz, 2007).

3.3.2 Treatment

Medicinal products may be indirectly released into the environment from waste treatment facilities (EFPIA, 2012) including incinerators, landfill sites or wastewater treatment plants because of the waste treatment shortcomings, which in general does not specifically target medicinal products. Medicinal products are widely detected in sewage treatment plants of several countries following excretions or direct disposal through the sink and toilets (BLAC, 2003) (Holm, 1995) (Maurer, 2007) (Vieno, 2007). In some cases, wastewater treatments can eliminate or remove a substantial amount of medicinal products residues, but there may still be significant concentrations of medicinal products in STEP effluents discharged into surface water bodies.

The percentage of medicinal product residues remaining in wastewater treatment very much depends on the substances considered and the technology implemented[32] (Igos, 2012) (Loos, 2012) as well as initial concentrations in the influents. For example, Ibuprofen which is present in significant amounts wastewater influents is destroyed at rates of 60 to 96% (Bendz, 2005), like Paracetamol[33] and codeine, while Carbamazepine is at rates of biodegradation of less than 10-30% (Joss, 2005) and beta-blockers are still significantly present in wastewater outlets. Jelic et al. (2012) compare concentrations of a number of medicinal products in wastewater influents and effluents, thus assessing treatment efficiency.

Different removal rates can be observed for various substances undergoing the same treatment. Those results highlight notable differences in the effectiveness of sewage treatment depending on the molecule. For instance, Okuda et al (Okuda, 2008) showed that the total concentration of individual medicinal products in the influent was efficiently removed by 80% during a biological treatment, but removal efficiencies of Carbamazepine and crotamiton were less than 30%. On the other hand, some treatments present similar rates of removal. FP6 Neptune project[34] shows for example that membrane bioreactor, biofilter and conventional plant present a comparable removal for most APIs, and that these compounds are only partially removed. It also shows that treatments involving sorption to sludge is generally relevant for few compounds[35] (e.g. for selected antibiotics such as Ciprofloxacin or Nor-floxacin and for some steroid estrogens (Loos, 2012)) and that treatment involving degradation often achieves only partial removal.

Different removal rates can also be observed between different treatments for the same mix of medicinal products. The total concentration of the individual medicinal products in the effluent

[32] More expensive than conventional water treatment, advanced water treatment enable to increase the elimination/removal of drug residues from the STEP effluents.
[33] Interview with Ake Wennmalm, professor and former environmental director for Stockholm County Council, carried out in the context of the present study.
[34] Neptune workshop: Technical Solutions for Nutrient and MicropollutantsRemoval in WWTPs UniversitéLaval, Québec, March 25-26, 2010. www.eu-neptune.org/Worksop/index_EN
[35] Mass balance calculations to estimate the fate of contaminants during wastewater treatment, including sorption to sludge showed that usually less than 2% of the total mass load of pharmaceuticals is removed by sorption. For most pharmaceuticals (including Carbamazepine, Sulfamethoxazole, and Trimethoprim) adsorption to sludge is negligible (Loos, 2012).

from CAS (conventional activated sludge (CAS)) process was 1.5 times higher than that from BNR (process biological nutrient removal) (Okuda, 2008). Furthermore, the total concentration of the individual medicinal products in the discharge from WWTPs applying ozonation following activated sludge process was reduced to less than 20%. Ozonation process followed by biological activated carbon process could efficiently reduce all the residual medicinal products below their quantification limits. Disinfection with ozone may have an added benefit of removing PPCPs and other micro-contaminants from the wastewater.

Beyond the type of treatment or combination of treatments (conventional or advanced), the conditions of treatments influence the removal rate. In the case of secondary treatments for instance, poor removals are observed in WWTPs with HRTs (hydraulic retention time) <15 h. Sludge retention time (SRT) does not seem to affect the removal rate. Redox conditions selected for BNR (Biological nutrient removal (BNR) with filtration and UV disinfection) may affect removals of some PPCPs. Furthermore, season has an impact on removals of some PPCPs: treatment in summer increased removals for some PPCPs.

Differences between sewage treatment plants and active substances are to be expected, and chemical fate models can be used to estimate the transformation reactions and the partitioning behaviour of medicinal products and personal care products (PPCPs) in sewage treatment plants (STPs). Modelling provides both qualitative and quantitative estimates for PPCP removal (Adams, 2008). In the specific case of epidemic or pandemic situations however, the massive administration of medicinal products may have a different behaviour in sewage treatment than in normal situation, and result in higher releases than "annually averaged emission".

When a substance is not detected in STEP effluents, it does not necessarily mean it has actually been eliminated. Some substances may be degraded into transformation products that are not monitored. For instance, concentrations of guanyl-urea (the metabolite of Metformin) are often higher than concentrations of Metformin itself[36]. Other substances may adsorb to sewage sludge (e.g. antibiotics), of which subsequent use in soil causes further risks of emissions into the terrestrial and aquatic compartments (Boxall, 2002) (Boxall, 2006) (Boxall, 2007a). Depending on the disposal/reuse practices of sludge in the MS, possible emissions into the environment through these pathways may be more or less significant. For example, in the case of land-filling of waste containing medicinal products, sewage sludge may be the origin of emissions having similar or even higher concentration of contaminants than those found in wastewater treatment plant sewage (BLAC, 2003) (Halling-Sørensen, 1998) (Maurer, 2007) (Vieno, 2007).

A number of MS have made significant progress in the development of advanced treatment techniques, e.g. Switzerland, Germany and Sweden[37].

In addition to questioning wastewater treatment efficacy, releases of medicinal products in the natural environment could also be due to sewage overflow caused by local conditions (e.g. rain events) (Rodriguez del Rey, 2012).

As for solid waste, despite the numerous efforts underway to find alternatives to incineration (Smith, 2002) at the international level, incineration can still be perceived as a more effective and environmentally sound way to handle environmental pollution from medicinal products than

[36] Comment from a representative from NL-RIVM.
[37] Comment from a representative from Sweden.

land-filling (Eckel, 1993) (Holm,1995) (Ahel, 2001). Depending on the nature of the packaging and the pharmaceutical product, as well as the technology used, medicinal products waste may either enter the high-calorific or medium-calorific waste fraction intended for incineration (e.g. tablet packaging), or the fraction intended for land-filling (e.g. glass bottles), or the effluent from the mechanical-biological treatment plan.

In theory, emissions into the environment from incineration are *a priori* considered negligible because of the environmental legislation regulating the treatment of incinerator smoke (Académie Nationale de Médecine, 2008). However, in practice, official quantification or estimation of these emissions is lacking and only partial studies exist about gaseous emissions of cytostatic medicinal products after incineration or co-incineration in hospital conditions (Académie Nationale de Médecine, 2008), which are sometimes contradictory. Some tests showed that almost the totality of anticancer medicinal products contaminating municipal waste could be eliminated through their incineration at 850°C for 2.2 seconds (Bisson, 1996). They therefore questioned the relevance of World Health Organisation (WHO) guidelines which promote the incineration of anti-cancer medicinal products beyond 1 000 °C to 1 200 °C. However, these tests where shown not to guarantee the elimination of specifically concentrated cytostatic products (e.g. in the case of unused medicinal products) (ADEME, 2004). Furthermore, other tests showed that anti-cancer medicinal products incineration did not modify mutagenic and genotoxic properties of the incineration residues (ADEME, 2004).

As for landfilling, examples exist where landfills accepting sewage sludge can produce leaching carrying high concentrations of medicinal products, similar or even higher than those found in wastewater treatment plant influents (more than several mg/L) (BLAC, 2003). Over a period, researchers Holm et al. found antibiotics and barbiturates (from 0.7 ppm up to 18 ppm) in a 45-year old Danish landfill (Halling-Sørensen, 1998). Landfills without leachate collection (e.g. from household waste) may therefore represent locally significant sources of pharmaceutical discharges into the environment (GACE, 2007). There have been no studies to investigate what happens to medicinal products in mechanical-biological treatment plants.

The potential environmental pollution by the waste from the manufacturing of medicinal products is an issue in the context of globalisation, since waste from medicinal products manufacturing can be treated in other countries (Läkemedelsverket, 2009), which do not necessarily run appropriate disposal facilities. This globalisation issue, which adds complexity to the evaluation, needs also to be considered, since even if not directly linked to impacts on the EU territory, it involves EU activity's environmental impacts.

3.3.3 Reuse of organic waste from sewage sludge and manure

The reuse of sludge and/or manure, which may be contaminated by human and veterinary medicinal products, may also be a source of emissions during the consumption phase of the life cycle. The hydrophilic nature of some compounds can lead to transfers of active molecules from soils to surface water or groundwater. So far, sewage sludge has been contaminated more by the human medicinal products compared to the veterinary ones. However, sewage treatment plants

might start using manure as an extra source of nutrients in their sewage, which means that also veterinary medicinal products might reach the environment through this route.

Statistics on sewage sludge production are for MS are presented in Table 2. The highest sludge production was observed in Germany, UK, Spain, France, Italy and Poland. These countries contribute to approximately 70% of total sludge produced in EU. The smallest sludge producer in EU is Malta. It should be mentioned that Poland, Hungary and Czech Republic contribute to more than 70% of produced sludge in the new Member States.

Using untreated organic waste as fertiliser might also contribute to the presence of medicinal products in ground water and in the ecosystem. A study (Kumara, 2005) showed that antibiotics in manure could be taken up by plants when they are fertilised with animal raw manures containing antibiotics. The three crops (corn, onion, cabbage) absorbed Chlortetracycline (2-17 ng/g fresh weight), but not Tylosin. Composting the organic waste generally lowers the medicinal products level by between 50 to 90% from the original concentration. Cessna et al. (2011) even show that less than 7% of the amount of tetracyclines, sulfonamides and macrolides initially present in manure could remain after composting period. Only a very few very persistent medicinal products survive the composting process. For example, the antibiotic substance Sulfamethazine was shown to resist degradation (0% reduction) in several composting processes (Dolliver, 2008), whereas Chlortetracycline level is reduced by 99% or Momensin and Tylosin level reduction ranged from 54 to 76% following the composting treatment. Key factors of influence include the consumed volume of the specific medicinal product, its metabolised fraction, the use rate of manure and sewage sludge, biodegradation and the absorption rate of the specific medicinal product in the sludge.

Some medicinal products (e.g. propranolol hydrochloride) can inhibit the anaerobic digestion performed during biogas production through blocking microorganisms' activity (Fountoulakisa, 2008). However, the use of the sludge pre-treatments prior to the anaerobic digestion process led to higher biogas productions and organic matter removal efficiencies in both mesophilic and thermophilic conditions (Carballa, 2006).

Trends in disposal and/or reuse of organic waste allow providing a picture of emissions through these contamination pathways (Kelessidis, 2012). A decline in landfill is a common trend for all MS, which will lower the amount of medicinal products able to leach to ground water. A few MS such as France and Malta will have increasing agriculture use of sewage sludge and thus probably an increasing amount of medicinal products in ground water. Countries such as Austria, Portugal, Slovakia, Hungary, Belgium, Latvia, Denmark, Ireland and Luxembourg will have increasing incineration of activated sludge and therefore fewer medicinal products will probably reach the ground water.

Table 2: Sewage sludge production, % of reuse, compost and land-filling and trends in the period of 2000 to 2009 (Kelessidis, 2012; Eurostat[38])

EU-15	9806	21.9	40						
Austria	254 (2006)	30.8 (2006)	17	21	6	4	-5	-5	-
Belgium	103 (2004)	10.8 (2004)	14	27	0	3	0	-19	↓
Denmark	140 (2007)	26.0 (2007)	59	19	4	-1	0	4	-
Finland	148 (2005)	28.2 (2005)	3	97	0	-9	17	-6	↓
France	1059 (2004)	17.0 (2004)	48	24	8	-3	20	-16	↓
Germany	2170 (2005)	26.3 (2005)	28	18	3	-4	-8	-6	↓
Greece	115 (2005)	10.5 (2005)	1	36	17	-2	-1	-56	↓
Ireland	60 (2005)	14.6 (2005)	70	25	5	28	0	-44	(↓)
Italy	1053 (2005)	18.1 (2005)	22	20	41	-4	-10	12	-
Luxembourg	14 (2003)	27.8 (2003)	56	34	0	-15	22	-18	↓
Netherlands	348 (2005)	22.0 (2005)	0	12	4	0	2	-14	↓
Portugal	189 (2007)	18 (2007)	85	8	7	71	0	-77	(↑)
Spain	1121 (2005)	26.0 (2005)	62	16	18	11	0	-2	↑
Sweden	210 (2005)	23.3 (2005)	24	34	1	8	2	-12	-
UK	1771 (2005)	29.5 (2005)	69	10	6	13	1	-3	↑
EU-12	1151	11.5	17						
Bulgaria	42 (2005)	5.4 (2005)	37	28	36	36	0	-72	(↑)
Cyprus	7 (2005)	11.1 (2005)	50	38	0	50	38	-100	↓
Czech Republic	172 (2005)	16.8 (2005)	48	32	12	-28	31	-9	↓
Estonia	29 (2005)	22.1 (2005)	0	79	21	-10	74	4	↓
Hungary	184 (2004)	18.2 (2004)	58	10	29	31	-20	-16	↑
Latvia	27 (2005)	12.5 (2005)	41	10	0	13	4	-38	(↑)
Lithuania	66 (2005)	19.1 (2005)	32	8	10	23	9	-78	(↑)
Malta	0.1 (2005)	0.1 (2005)	0	0	100	0	0	0	
Poland	486 (2005)	12.7 (2005)	21	0	0	8	-3	-28	↓
Romania	68 (2005)	3.1 (2005)	0	20	73	0	20	-27	↓
Slovakia	56 (2005)	10.5 (2005)	0	68	23	-63	67	-1	↓
Slovenia	14 (2005)	6.8 (2005)	1	0	19	-3	-11	-67	↓
EU-27	10957	17.7	37						

[38] It should be mentioned that in many cases, there is unevenness among countries' data concerning the use of terms. For instance, composting is often included in agricultural utilisation and vice versa.

Some countries such as Sweden, Czech Republic, Lithuania, Poland, Romania, Slovenia, and UK will increase the amount of composting of activated sludge, which will lower the amount of medicinal products in sludge significantly.

3.4 Chapter summary

3.4.1 Key messages

- In the EU, the contribution of manufacturing facilities to emissions of medicinal products and/or their residues is generally considered negligible. However, possible pollution downstream from manufacturing plants has been observed in the EU while monitoring specific sites. Compared to the consumption stage, pollution at this stage may be considered more localised and occasional.
- The consumption of both veterinary and human medicinal products significantly contributes to the emission of medicinal products through excretions, either entering directly the environment (diffuse contamination) and/or released into the sewage network (point source pollution). Excretions are the major known contamination pathway. Veterinary medicinal products can also enter directly the environment through food/feed surplus, notably in aquaculture.
- Releases of medicinal products also occur through the incorrect disposal of unused medicines through the sinks and toilets. Although contamination does not seem to reach the same extent as pollution from excretions, it is not negligible and a large share can be avoidable.
- Wastewater treatments can eliminate or remove a substantial amount of medicinal product residues, but there may still be detectable residual emissions of some medicinal products.
- Some substances tend to adsorb to sewage sludge, of which subsequent use for soil amendment results in further risks of emissions into the environment. More precisely, the risk concerns the persistent medicinal products that resist biodegradation during the aerobic or anaerobic treatments of the sludge. The hydrophilic nature of some compounds can lead to transfers of active molecules from soils to surface water or groundwater by the phenomenon of mobility.
- The reuse of organic waste, through sludge and manure spreading, contaminated by human and veterinary medicinal products, may also be a source of emissions.
- Composting the organic waste lowers generally the medicinal products level by between 50 to 90% from the original concentration.
- Landfills accepting sewage sludge can produce leaching carrying significant concentrations of medicinal products, similar or even higher than those found in wastewater treatment plant inflows.

3.4.2 Knowledge gaps

- There is a need to improve monitoring strategies to characterise the emissions of medicinal products from different facilities (households, hospitals, health care centres, wastewater treatment plants, incineration facilities, manufacturing sites, etc.) and centralise the information in a standardised format. This is a prerequisite to be able to compare and analyse information related to the emission of medicinal products in the environment, and ultimately assess whether there is or not an acceptable risk for the environment.
- To date, significant amount of work has been made in the EU about the removal and degradation of medicinal products at wastewater treatment plants, through practical experience and modelling. However, knowledge is still scarce regarding the benefits of additional treatment steps, in particular relatively to their additional costs.
- There is a need to better consider, model and quantify the potential release from different veterinary practices (stocking, application form, manure, composting, etc.).

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Chapter 4: Which molecules are found in the environment and how do they behave?

Medicinal product residues of various categories (hormones, anti-cancer, antidepressants, antibiotics, etc.) have been detected in all environmental compartments, including sewage water, surface water, groundwater, soil, air and biota (Heberer, 2002) (Kümmerer, 2009) (Kümmerer, 2008) (Halling-Sørensen, 1998) (Touraud, 2011) (Willimas, 2005) (Buerge, 2006) (Ternes, 2001) although data on soil, air, biota are still scarce. The detected concentrations are in the range of sub-ng/L levels to more than the µg/L level, see reviews and compilations (Bergmann, 2011) (Debska, 2004) (Kinney, 2006) (Segura, 2009) (Jurado, 2012) (Lapworth, 2012) (Loos, 2010). Nevertheless, the monitoring of such molecules in the environment is limited by a metrological lack (limitations in the routine analytical methods available). Box 1 highlights key publications related to the presence, fate and behaviour of medicinal products in the environment.

Box 1: Key publications including monitoring data of medicinal products in the environment

Oldenkamp R, Huijbregts MAJ, Hollander A, Vesporten A, Goossens H, Rajas MJ. (2013) Spatially explicit prioritisation of human antibiotics and antineoplastics in Europe. *Environment International*, 51: 13-26.

Hughes SR, Kay P, Brown LE. (2013) Global Synthesis and Critical Evaluation of Pharmaceutical Data Sets Collected from River Systems. *Environmental Science and Technology*, 47:661-677.

Fick J, Söderström H, Lindberg RH, Phan C, Tysklind M, Larsson JDG. (2009) Contamination of surface, ground and drinking water from pharmaceutical production. *Environ Toxicol Chem*, 28:2522-2527.

ter Laak TL, van der Aa M, Houtman CJ, Stoks PG, van Wezel AP. (2010) Relating environmental concentrations of medicinal products to consumption: A mass balance approach for the river Rhine. *Environment international,* 36: 403-409.

German Advisory Council on the Environment (GACE). (2007) Medicinal products in the environment: Presents p.15 the Maximum pharmaceutical concentrations in bank filtrate, surface waters and sewage treatment plant effluent; p.17 the maximum concentration levels of various antibiotics measured in agricultural (top) soils fertilised with conventional organic fertilisers.

Zuccato E, Castiglioni S, Fanelli R. (2005) Identification of the medicinal products for human use contaminating the Italian aquatic environment," *Journal of Hazardous Materials*, 122:205–209. This publication indicates the medicinal products concentration found in water and sediments in Italy for 10 medicinal products of interest.

Ségura P, François M, Gagnon C, Sauvé S. (2009) Review of the occurrence of anti-infectives in contaminated wastewaters and natural and drinking waters. *Environmental health perspectives*, 117:675–84.

KNAPPE project (2008). Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters. Final report, available at: environmentalhealthcollaborative.org/images/KNAPPE_REPORT_FINAL.pdf

Loos R, Negrão De Carvalho R, Comero S, Conduto ADS, Ghiani M, Lettieri T, Locoro G, Paracchini B, Tavazzi S, Gawlik B, Blaha L, Jarosova B, Voorspoels S, Schwesig D, Haglund P, Fick J, Gans O. (2012) EU Wide Monitoring Survey on Wastewater Treatment Plant Effluents . JRC Scientific and Policy Reports.

Several research papers show that the active pharmaceutical ingredients detected in the environment include medicinal products put on the market several decades ago (GACE, 2007) (Rönnefahrt, 2002) (see also the Annex), but also newer medicines are detected. Notably a recent paper (Hughes, 2013) highlights the dataset collected from river systems at global level. For instance, the synthetic oestrogen 17-α-Ethinylestradiol (EE2) is one of the few medicinal product substances for which significant extents of absorption to sludge have been documented (Ternes, 2002) (Caldwell, 2010). EE2 has been detected in sewage treatment plant effluents in low nanogram-per-litre (ng/l) levels and occasionally also in surface waters and drinking water in e.g. the United States, UK, Canada, Brazil and Germany.

It has to be noted that even if concentrations found in the environment are at generally low levels, medicinal products are developed to be highly potent substances and thus concentration levels on its own are not the precise indication of the associated risks. Indeed, this risk is a combination between a hazard and an exposure, so it depends on the nature of the substance (toxicity of compound, toxicity of metabolites, degradability, etc.), the duration of exposure and other exposure characteristics (media physic-chemical properties, etc.).

While some information exists on active substances[39], less information is available on the environmental occurrence and fate of their metabolites and transformation products due to knowledge gaps on their behaviour (e.g. persistence, degradation and reactivation behaviour) in the environment (GACE, 2007), and/or detection issues.

The environmental concentrations of medicinal products are variable, both geographically and seasonally due to local practices (Vystavna, 2012) and environmental factors (e.g. dilution rate, molecule's affinity for different compartments, precipitations rate) (ter Laak, 2010) (KNAPPE, 2008) (Ternes, 2001). In the Netherlands for example, the environmental load of Diclofenac and Ibuprofen has been found to be 10 times higher in winter than in summer (RIWA, 2010).

The majority of concentration data concerns the aquatic environment. Indeed, nearly no data in air are available because concentrations in air are considered negligible. There is an increasing amount of terrestrial data but there are more technical difficulties to detect medicinal products in soils and sediments than in aqueous media (GACE, 2007).

A relatively large number of data are available concerning drinking water (see Box 2).

Box 2: Key publications including monitoring data of medicinal products in drinking water

ANSES (2011) National analysis campaign on drug residues in water intended for human consumption. www.anses.fr/en/content/national-analysis-campaign-drug-residues-water-results-line-expectations

Vulliet E, Cren-Olivé C, Grenier-Loustalot MF. (2009) Occurrence of medicinal products and hormones in drinking water treated from surface waters. *Environmental Chemistry Letters,* 9:103-114.

Fick J, Söderström H, Lindberg RH, Phan C, Tysklind M, Larsson JDG. (2009) Contamination of surface, ground and drinking water from pharmaceutical production. *Environ Toxicol Chem,* 28:2522-2527.

Mompelat S, Le Bot B, Thomas O (2009) Occurrence and fate of pharmaceutical products andby-products, from resource to drinking water. *Environ Int*, 35:803–814.

[39] Because of their large use, identified hazard or their use as marker substances for the discharge of pharmaceuticals into the environment

World Health Organisation (2011) Medicinal products in Drinking water. www.who.int/water_sanitation_health/publications/2011/medicinal products_20110601.pdf

Ségura P, François M, Gagnon C, Sauvé S. (2009) Review of the occurrence of anti-infectives in contaminated wastewaters and natural and drinking waters. *Environmental health perspectives*, 117:675–84.

Touraud E, Roig B, Sumpter JP, Coetsier, C. (2011) Drug residues and endocrine disruptors in drinking water: Risk for humans? *International Journal of Hygiene and Environmental Health,* 214: 437-41.

Mompelat et al. (2009) performed a systematic review on the occurrence of medicinal products in drinking water. In doing so, 17 pharmaceutical products and 5 by-products have been found between 1.4 and 1 250 ng/L (with highest concentrations for iodinated contrast media, diatrizoate and the metabolite AMDOPH) (Perez, 2007) (Heberer, 2004) (Reddersen, 2002). The molecules most often detected in Germany, France, Finland are non-steroidal anti-inflammatory medicinal products (NSAIDs) and to a slight extent anti-convulsants. Likewise, ANSES (in France) investigated the presence of these substances in water intended for human consumption and launched a national campaign to measure 45 pharmaceutical substances of human or veterinary origin, or their metabolites, in surface and groundwater (ANSES, 2011). The molecules most frequently found included Carbamazepine (an anti-epileptic medicinal product) and its main metabolite, as well as oxazepam (an anxiolytic) which is both a parent product and a benzodiazepine metabolite.

In Sweden, a monitoring programme has been performed on 101 medicinal products on more than 100 samples. The sampling programme was focused on diffuse emissions from urban areas reflected in samples from wastewater treatment plants (WWTPs) and their receiving waters, biota samples (perch) from two background lakes and drinking water from two cities. Of the 101 medicinal products included, 92 were detected in the WWTP influent of at least one WWTP in levels that ranged from low ng/L up to 540 g/L, with a median concentration of 53 ng/L. Sixty-six medicinal products were detected in the surface water samples in the range from low ng/L up to 1.8 µg/L. Twenty-three medicinal products were detected in seven biota (perch) samples. Low levels (low ng/L range) of 26 medicinal products were detected in drinking water samples (Fick, 2009).

Vulliet et al. (2009) analysed the presence of medicinal products including hormones in French drinking waters: 27 of the 51 target compounds were detected at least once in surface waters, which are sources of drinking water. The highest concentration was observed for Paracetamol (71 ng/L) but concentrations rarely exceeded 50 ng/L. As for the frequency, Carbamazepine and atenolol were present in more than 30% of the samples. Progestagens and androgens seemed to be the more resistant to drinking water treatments.

Beyond the dilution inherent to the natural environment, the low detected concentrations can be explained by the dilution that occurs in sewage networks (e.g. a dilution by at least a factor of 100 of hospital wastewater by municipal wastewater as been reported (Kümmerer, 2010)) and by the elimination/removal of substances during water treatments process (Heberer, 2002) (GACE, 2007). Higher concentrations of medicinal products have however been observed, for example in rivers downstream wastewater treatment plants. In Norway, the input from a local manufacturer was much higher for a certain antibiotic than inputs originating from hospitals and the general public (Thomas, 2008).

Medicinal products can be transferred from one environmental compartment to another, for example from wastewater to sludge or sediments, or from soils to water bodies. This transfer

depends on various factors (e.g. nature of the molecule, polarity, absorption behaviour, type of sediment, pH, content of organic substance, water saturation and aerobic properties) (Mersmann, 2003), and processes including extent of degradation, partitioning and characteristics of the receiving environment. For some medicinal products, sorption coefficients for soils and sediments are highly variable and, differently from other chemicals, depend on rather on pH and ionic strength than on soil carbon content (Boxall, 2002). The sorption rate also influences the rate of transportation, thus non-sorptive medicinal products (e.g. sulphonamides) are quickly transported to surface water and groundwater while sorptive substance are much slower transported (Holten-Lützhøf , 1999).

Medicinal products can degrade biotically or abiotically in soils and water, a process that will in general reduce their potency, even if some degradation products are also hazardous (Halling-Sørensen, 2002). Degradation rates might be significantly affected by environmental factors such as temperature, pH, and soil type (notably on sorption) and the nature of the considered compound. For instance, when considering veterinary medicinal products, some molecules rapidly degrade (e.g. Tylosin, Diazinon) while other are moderately (e.g. Ivermectin) or highly persistent (e.g. Sarafloxacin).

The distribution to biota and accumulation throughout the food chain is poorly understood, in particular because of the lack of adapted models[40]. Indeed, many medicinal products are polar compounds and ionise/dissociate more than well studied environmental xenobiotics[41] in addition to be less lipophilic[42], which make the existing bioaccumulation models inappropriate for modelling the fate of medicinal products through the trophic chain.

Thus, there is a lack of knowledge and experimental evidence, which does not permit conclusions on bioaccumulation mechanisms.

The available data regarding the bioaccumulation of medicinal products mainly concerns the ability to bio-concentrate of hormones and a reduced number of specific medicinal products in fish plasma, adipose and muscles. It has to be noted that inter-site variations have been observed suggesting that chemical characteristics of effluents and/or recipient waters strongly affect the uptake/bioconcentration of medicinal products in fish. Fick et al. (2010) measured plasma concentration of 25 medicinal products in rainbow trout exposed for 14 days to sewage effluents in Sweden and found that Levonorgestrel concentration exceeded the human therapeutic plasma level. Brown et al. (2007) reported the uptake of NSAIDs and Gemfibrozil into rainbow trout blood plasma through sewage effluents exposures. Al-Ansari et al. (2010) have detected Ethynylestradiol EE2 in wild fish collected downstream of Canadian municipal effluents at average concentration of 1.5 ng/g. EE2 could be a potential candidate for bioaccumulation in higher predators, especially bottom feeding fishes. More generally, LIF, initiator of the Sweden environmental classification of medicinal products, highlights the potential of highly lipid-soluble medicinal products to bioaccumulate in the fat tissue of animals and bioaccumulate throughout the food web (LIF, 2010).

[40] Identified as one of the main research needs at ECETOC workshops (www.ecetoc.org/workshop-reports)
[41] Foreign to the body or to living organisms.
[42] Having an affinity for lipids

4.1 Chapter summary

4.1.1 Key messages

- Medicinal product residues of various types have been detected or estimated in all environmental compartments, and mostly in aqueous media, including drinking water.
- Several EU Members States have voluntary initiatives of monitoring environmental concentrations of medicinal products in aquatic environment and/or in wastewater and drinking water.
- Active pharmaceutical ingredients are present in the environment at concentrations ranging ng/l–µg/l. The environmental concentrations of medicinal products are variable, both geographically and seasonally due to local practices and environmental factors.
- Medicinal products could be detected in drinking waters, usually at low concentrations (ng/L range). The molecules most often detected in Germany, France, Finland are non-steroidal anti-inflammatory medicinal products (NSAIDs). Progestagens and androgens seemed to be the more resistant to drinking water treatments.
- The APIs detected in the environment include medicinal products put on the market several decades ago as well as new medicines.
- Medicinal products can be transferred from one environmental compartment to another, depending on various factors and processes. Their mobility in soil, determined by their affinity to the organic particles (Koc), namely influences their transfer into aquatic compartments, through drainage waters (for substances with low Koc) or through their association with eroded soil or sediment particles in run-off waters (for substances with high Koc).
- Medicinal products can degrade biotically or abiotically in soils and water, a process that will in general reduce their potency, even if some degradation products are also hazardous.
- Highly lipid-soluble medicinal products may have the ability to bioaccumulate in the fat tissue of animals. The presence of medicinal products was detected in fish species (rainbow trout, wild fish) exposed to sewage effluents. Some substances, such as EE2, could be potential candidates for bioaccumulation in higher predators.

4.1.2 Knowledge gaps

- More data are required to assess the concentrations and fate of medicinal products in the environment (surface and ground water as well as in soil and biota) and in drinking water, notably for veterinary medicinal products. The existing data should be collected and a rather harmonised approach / strategy to measure and collect

data are urgently needed. Moreover, after harmonisation, there will be also a need to analyse all the data collected.

- Scarce information is available on the environmental occurrence and fate of medicinal products metabolites and transformation products due to knowledge gaps on their behaviour in the environment, and/or detection issues. There is both a need to develop (i) more sensitive analytical methods for detection of metabolites in the environment; and (ii) other methods for increasing the knowledge on the fate of medicinal products and metabolites in the environment.
- Knowledge is scarce on the medicinal products distribution in biota and accumulation throughout the food web.
- The knowledge on biodegradation in manure and slurry is limited to a small number of medicinal products, and often restricted to the dossiers.
- The absorption of pharmaceutical products in wastewater treatment plants solids needs further study, in order to understand if they can be released back into the environment.

Chapter 5: Environmental hazards

The whole range of standard and advanced ecotoxicological techniques may be applied to medicinal products to describe their modes and mechanisms of action in non-target organisms. These techniques can be used to identify suitable ecotoxicological endpoints on the molecular, individual, population and ecological level of biological complexity, to understand their transformation in exposed organisms, and finally to quantify ecotoxicological thresholds (NOECs, NOELs, PNECs) using ecotoxicological data from various levels of biological complexity, for compilations see recent reviews, special issues and books (Henderson, 2009) (Brooks, 2012) (Brausch, 2012) (Rosi-Marshall, 2012) (Huerta, 2012) (Knacker, 2010).

The widespread occurrence of medicinal products in the environment (see chapter 4) obviously begs the question whether realistic concentrations might pose a risk for exposed biota. The decline of vulture populations on the Indian sub-continent due to poisoning with Dicloflenac, a non-steroidal painkiller, is probably the most prominent case demonstrating that the exposure to medicinal products can lead to severe ecotoxicological effects. The birds were exposed by feeding on carcasses that originate from cattle previously treated with Diclofenac and then died of kidney failure (Risebrough, 2004) (Oaks, 2004). It has to be noted however that this exposure pathway has to be considered as a specific example, which will be highly improbable in Europe.

Other examples of ecotoxicological effects of medicinal products at environmentally realistic concentrations include the contraceptive Ethinylestradiol (EE2) which impairs the reproduction of exposed fish populations (Nash, 2004) (Jobling, 2003) (Bjerregaard, 2008); the anti-mycotic agent Clotrimazole[43] which affects algal communities at picomolar concentrations (Porsbring, 2009; OSPAR 2013); the effects of various antibiotics on environmental bacteria and algae (Brosche, 2010) (Halling-Sørensen, 2000) (Halling-Sørensen, 2002); the impacts of the Benzodiazepine anxiolytic drug Oxazepam on European perch (Brodin, 2013); and the effects of the anti-parasiticide Ivermectin on dung fauna (Liebig, 2010). In Sweden, measured surface water concentrations of medicinal products were evaluated in 2010 by comparing them to critical environmental concentrations, i.e. the water concentration that is expected to cause a pharmacological effect in fish. This evaluation showed that five medicinal products in these samples are expected to cause a pharmacological response in fish exposed to these waters (Fick, 2011).

On the other hand, in a number of other ecotoxicological studies it was concluded that clear ecotoxic effects of the investigated medicinal products are only to be expected at concentrations well above environmentally realistic levels. Hence, in several studies the current risk to the environment has been assessed as minor or negligible (Miege, 2006) (Wilson, 2004) or limited to certain situations (Lienert, 2007b) (Brain, 2006).

[43] The OSPAR report indicates an inhibition of algal 14á-demethylase already at environmental concentrations. The OSPAR report states that this point would merit to be studied in more detail with realization of single tests species for example. Before that, this result cannot be used to calculate the PNEC but it should be taken into account for "T" criteria evaluation.

These seemingly contradictory findings reflect the complexity of the issue, which makes it hard to identify general rules or overarching patterns. Instead, the problem of "medicinal products in the environment" decomposes into a series of highly specific cases, characterised by the different bioassays and endpoints used for the ecotoxicological hazard characterisation, different exposure pathways and concentrations, enormously different characteristics of the assessed medicinal products (in particular their ecotoxicological modes and mechanisms of action and environmental fate) and the lack of publicly available ecotoxicological data even if compounds have been on the market for several years (Carlsson, 2006) (Crane, 2000) (Stuer-Lauridsen, 2000), as an environmental risk assessment was not mandatory during the market authorisation process at the time. Even if chronic studies have been performed e.g. during the market authorisation of new drugs, the results are often confined to the authorisation dossiers, i.e. the information is not available for independent review or a meta-analysis. This resembles the pre-REACH situation for industrial chemicals, which were divided into so-called "existing chemicals" (on the market prior to 1981, for which no risk assessment was required) and "new chemicals" (for which a risk assessment was mandatory).

The complexity of the issue and the need for specific, case-by-case judgements is highlighted by the recent analysis by Bergmann et al. (2011), who calculated risk quotients (MEC_{max}/PNEC ratios) for medicinal products for the aquatic environment. The risk quotient range from almost 10 000 for EE2 to less than 0.00001 for Cyclophosphamid, an anti-cancer drug, i.e. the values span over 9 orders of magnitude (Figure 6). That assessment factors of up to 25 000 had to be used indicates the enormous uncertainty and data gaps in the data on environmental hazards, which were often limited to one value on the acute toxicity to one species (16 out of 70 analysed compounds).

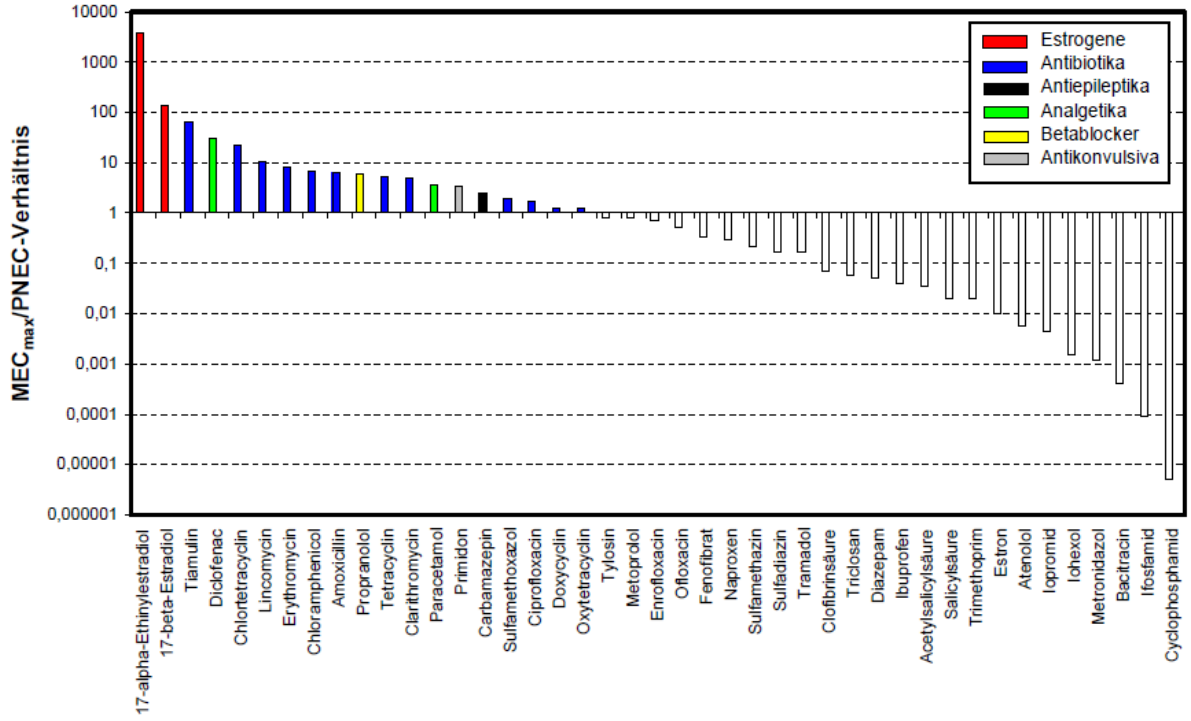

Figure 6: Risk quotients in Germany for a range of medicinal products (Bergmann, 2011).

This obviously calls for solid prioritisation strategies (Roos, 2012) (Besse, 2010) which are currently limited by the insufficient availability of high-quality data on the chronic ecotoxicity of medicinal

products, which has been repeatedly emphasised as a major gap by several authors (Crane, 2006) (Stuer-Lauridsen, 2000) (Carlsson, 2006) (Bergmann, 2011).

Similarly, data on the occurrence of medicinal products in the environment are scattered and usually limited to specific case studies, often driven by specific academic research projects. Routine chemical monitoring programs organised by MS authorities usually do not consider pharmaceutical substances, or are limited to only a very few representatives. Negotiations on the recent proposal from the European Commission to include three pharmaceutical substances (Diclofenac, 17α-Ethinylestradiol, 17ß-Estradiol) in the list of priority pollutants under the Water Framework Directive led, in April 2013, to a provisional agreement to put them instead on a "watch list", with the aim of gathering monitoring data "for the specific purpose of facilitating the determination of appropriate measures to address the risk posed by those substances". If the text is finally agreed upon, MS will be obliged to monitor the three medicinal products at least annually at a limited number of representative monitoring stations for up to four years, but no restrictions will be put in place. Environmental quality standards could still be set for the substances during the next review of the priority substances list (ENVI, 2012).

Medicinal products are by their very nature biologically highly active chemicals. Antibiotics, anti-parasiticides, anti-mycotics and a large proportion of anti-cancer drugs are intended to kill their target organism or target cells. From an ecotoxicological perspective, these compounds hence closely resemble pesticides and biocides. In fact, imidazoles are for example simultaneously used as medicinal products (anti-mycotics) and as plant protection products (fungicides). Moreover, Medetomidine, a veterinary sedative, as well as Ivermectin (Pinoro, 2011), an anti-parasiticide, are currently evaluated as antifouling biocides, the corresponding dossier for medetomidine (Selectope®) has recently been submitted to the competent authority in the UK.

Other pharmaceutical groups, such as hormones, antidepressants or painkillers, are intended to exert a specific effect in their target organism (human or animal), without exerting any lethal effects. Because of this, and because of their interaction with bio-synthetic pathways, especially human medicinal products have generally only a low acute (eco)toxicity: acute EC50 or NOEC values in standard short-term bioassays are often in the mg/l range, i.e. far above environmentally realistic concentrations. However, a sensible environmental hazard assessment has to not only consider specific mechanisms, such as e.g. endocrine disruption, but also other subtle non-lethal effects, caused by a chronic (life-long) exposure of target as well as non-target organisms, which might not be included within the tested species. In addition, although there are still substantial knowledge gaps to be filled in, research over the last decade has started to produce high quality data on the chronic ecotoxicology of both human as well as veterinary medicinal products. Recent reviews and data compilations can be found (Hümmerer, 2008) (Santos, 2010) (Daughton, 2011) (Brausch, 2012) (Molander, 2009). Still only very limited data is available about the potential environmental hazard of medicinal products to marine life, terrestrial and sediment dwelling organisms as well as in ecological contexts.

5.1 Using modes of action to assess the environmental hazard of medicinal products

Since EU legislation on medicinal products in the 2000's, medicinal products are put on the market only after extensive scrutiny of their modes and mechanisms of action on their intended molecular targets and target organisms, as well as toxicological side effects. Consequently it has been frequently suggested to leverage this knowledge also for ranking and prioritisation as well as environmental hazard and risk assessment of medicinal products and for the development of appropriate bio-analytical tools (Fent, 2006) (Escher, 2005) (Owen, 2007) (Runnalls, 2007) (Christen, 2010) (Brooks, 2009). For example, acknowledging the specific bacteriostatic or bactericidal mode of action[44] of antibiotics helps to focus environmental assessments using environmental bacteria or procaryotic algae as the most sensitive non-target species, a strategy that is already suggested in the current EU guidelines on the environmental risk assessment of medicinal products. The most prominent example of molecular receptors that are highly conserved in structure and function across species are perhaps the sex steroid receptors, which are the receptors for e.g. EE2 in humans but at the same time also drive environmental impacts, e.g. on fish populations (Nash, 2004) (Jobling, 2003) (Bjerregaard, 2008).

Consequently, Huggett et al. (2003) suggested a prioritisation scheme for assessing the impact of human medicinal products to fish based on a comparison between the expected concentrations in the blood plasma of fish (as a result of an exposure via the environment), and human therapeutic plasma concentrations (Schreiber, 2011). Such an approach depends on two critical assumptions whose validity has not been finally assessed for most medicinal products: (i) the therapeutic mode of action in humans is responsible for the toxicity in fish, (ii) the sensitivity of human and fish are highly correlated, i.e. similar blood plasma concentrations in humans, respectively fish, lead to similar concentrations at the target sites in both organisms.

The approach by Huggett et al., as well as similar read-across approaches, assumes a receptor in the environmentally exposed non-target organism that is largely homologous to the receptor in the target organism (i.e. humans) – which is why the approach has been developed for teleost species only. The original drug target receptor might not be present in an exposed non-target species, if it belongs to a more distant genus, e.g. bacteria, plants or invertebrate species. Medicinal products will therefore often have multiple mechanisms of action in the environment, depending on the considered species. EE2, for example, is obviously a highly specific oestrogen in fish, but was classified as a mere baseline toxicant of low toxicity in algae (Brooks, 2009). However, it would fall too short to conclude from the fact that a given target receptor is not present, that a certain pharmaceutical in general does only have a low toxicity, i.e. does not bind to any other receptor. For example, the beta-blocker Propranolol is 100 times more toxic to algae than expected from a simple baseline toxicity model (Escher, 2005b), although the intended molecular drug target (the adrenergic receptor) is not present in plants.

Even if the target receptor is present, its biological function can be vastly different from the function in the original target organism. The veterinary drug Medetomidine, for example, is a α2-

[44] the mode of action is the mechanism by which a pharmacologically active substance produces an effect on a living organism or in a biochemical system

adrenoceptor agonist that is used for sedating animals. However, activation of this receptor also affects fish pigmentation (Lennquist, 2010). Medetomidine also binds specifically to the invertebrate counterpart of the adrenoceptor, the so-called octopamine receptor (Lind, 2010), causing increased swimming activity in barnacle larvae and consequently inhibiting their settling on surfaces already at nanomolar concentrations (Dahlström, 2000).

Another example for a potential receptor that is conserved across a broad range of species, but exerts different physiological functions is the HMG-COA reductase (the molecular target of e.g. statins, a class of lipid-lowering medicinal products), which is the rate-controlling enzyme of cholesterol formation in mammals, but regulates egg production in the parasite *Schistosoma mansoni* (Vandewaa, 1989) and juvenile hormone production in invertebrates (Debernard, 1994).

In summary, read-across approaches that leverage the existing knowledge on modes of action from human pharmacology and toxicology might currently be most promising for assessing the fish toxicity of medicinal products that are intended to act on specific receptors in humans, see also the comparative assessment of Huggett's fish-plasma model that was recently carried out by Roos and coworkers (Ross, 2012). Such approaches might be more limited for medicinal products that are intended to act on other species (e.g. antibiotics and anti-mycotics). A particular problem might be the risk of false-negatives: a compound that, by virtue of its intended use and/or because of existing knowledge on its mode of action, is likely to interact specifically with relevant biological processes in the environment, can be easily flagged as a potential environmental hazard by read-across approaches. However, it cannot be easily concluded that a compound that does not possess such warning signals is environmentally benign.

In order to inform the environmental risk assessment of medicinal products, the ecotoxicologically relevant modes of action need to be considered in a systematic and unbiased manner. Such an approach has been outlined by Escher and co-workers) (Escher, 2005), but seems currently limited to investigations on photosynthesis, estrogen-receptor activation, general reactive toxicity and baseline toxicity. Additional ecotoxicological important modes of action include for example (but are not limited to) the inhibition of nitrification, interactions with chemical sensing (kairomones) and effects on the invertebrate hormone system (ecdysone, crustecdysone system).

5.2 Individual vs. population- and ecosystem-level effects

The pharmacological and toxicological impact of an exposure to medicinal products is typically evaluated on the level of individual human beings and human populations during drug development and post-marketing studies. Environmental hazards are usually described on the level of populations (using assays such as e.g. the inhibition of daphnia reproduction according to OECD test guideline 211). However, possible *ecosystem-level* consequences are to be evaluated during an environmental risk assessment, which is often achieved by using assessment factors. This implies that distinctions such as the ones put forward by Christen and co-workers (Christen, 2010) who grouped affected physiological pathways into "important" (e.g. estrogen receptor binding) and pathways of "minor importance" (e.g. effects on the central nervous system, blood pressure) need critical reflection, as functioning of the "minor important" pathways might actually be of critical importance for the ecological fitness of the affected species.

Similar to other chemicals, studies that investigate the effects of medicinal products on biological communities (biocoenoses) or under field conditions are comparatively rare, in particular because such studies are hardly ever required during the initial environmental risk assessment and are often prohibitively expensive. Recently a range of studies has been published that used natural microbial communities to study the effects of medicinal products, in particular antibiotics (Halling-Sørensen, 2002) (Lawrence, 2005) (Backhaus, 2011) (Verma, 2007) (Liu, 2011).

Microcosms that are more complex were used in the study by Richards and co-workers (Richards, 2004) on the effects of the serotonine re-uptake inhibitor Fluoxetine, the painkiller Ibuprofen and the antibiotic Ciprofloxacin. Results show that medicinal products can have ecological effects well below the equivalent pharmacologically active concentrations in mammals. Ivermectin, a commonly used veterinary anti-parasiticide was also evaluated in a microcosm study (Brinke, 2010), demonstrating that the compound might put exposed ecological communities especially in sediments at risk (realistic worst case risk quotient 1-36). A broad overview of the use of microcosms for improving the risk assessment for veterinary medicinal products was provided in 2005 by van den Brink and his colleagues (Brinke, 2010).

Munoz and co-workers (Munoz, 2009) used eco-epidemiological studies in the Llobregat river basin in order to analyse the environmental consequences of pharmaceutical exposure in the environment and suggest combining such approaches with laboratory-based community-level studies in order to improve risk assessment.

5.3 Mixture of medicinal products

Medicinal products do not occur as isolated, pure substances in an environmental compartment. As a broad range of different substances is used simultaneously in human and veterinary medicine in any given area, medicinal products are present as multi-component mixtures in the environment. Furthermore, most medicinal products will either be transformed by physical and chemical processes in the environment and/or taken up by some organism and subsequently bio-transformed. From an environmental perspective, even individual medicinal products ultimately have to be regarded as a multi-component chemical mixture (parent compound plus degradation products and metabolites).

In view of the widespread occurrence of medicinal products in all major environmental compartments and their inherent high biological activity, it is not surprising that stakeholders from government, industry and academia rank those compounds among the top 5 surface and groundwater contaminants that need additional management in the US and Europe(Doerr-MacEwen, 2006). Mixture effects have been named by the interviewees as one of the major sources of uncertainty, hampering appropriate management strategies. It has even been suggested by O'Brien and D. Dietrich (O'Brien, 2004) that the issue is so complex that it might be more economical to simply modernise existing sewage treatment plants in order to prevent the entry of pharmaceutical mixtures into the environment in the first place.

Not only is the occurrence as multi-component mixtures typical for the environmental exposure situation of medicinal products. Two characteristics also make their joint toxic effects a major issue for hazard and risk assessment (Kortenkamp, 2009):

1) the ecotoxicity of a mixture is almost always higher than the effects of its individual components; and
2) a mixture can have a considerable ecotoxicity, even if all components are present only in low concentrations that do not provoke significant toxic effects if acting singly on the exposed organisms.

Backhaus et al. (2011) demonstrated for example mixture effects exceeding 50%, respectively 15% inhibition, although the individual medicinal products (10 quinolone antibiotics in one case, 14 dissimilarly acting medicinal products in the other case) were present only at low, individually not significantly toxic concentrations. Significant mixture effects from low-effect individual concentrations (EC50) were also observed in a study by Fent and co-workers (Fent, 2006b) for a mixture of Cimetidine, Fenofibrate, Furosemide and Phenazone. A mixture of Fluoxetine and clofibric acid killed more than 50% of a water-flea (*Daphnia*) population after an exposure of 6 days, although the components were present at concentrations that did not provoke significant effects individually (Flaherty, 2005). In the same study, a significant shift in sex ratio was observed after an exposure to a three-component mixture of erythromycin, triclosan and trimethoprim - again at a mixture concentration at which all components were present at concentrations that did not provoke significant individual effects.

Current empirical knowledge unanimously shows that the toxicity of mixtures that are composed of medicinal products for which a similar mode or mechanism of action has been described in the target organisms can be predicted by applying the Concentration Addition (CA) concept (Kortenkamp, 2009) (Lawrence, 2005). Examples can be found for a mixture of 10 quinolone antibiotics (Backhaus, 1999), for mixtures of the anti-inflammatory drugs Diclofenac, Ibuprofen, Naproxen and Acetylsalicylic acid in a study with daphnids and algae (Cleuvers, 2003), as well as for mixtures of the ß-blockers Propranolol, atenolol and Metoproplol (Cleuvers, 2005). In addition, studies with binary mixtures of selective serotonin re-uptake inhibitors Citalopram, Fluoxetine, Fuvoxamine, Paroxetine and Sertraline did not find any significant deviations from CA-expected mixture toxicities in studies with algae and daphnids (Christensen, 2007). Estrogenic mixture effects of Furosemide and 17ß-estradiol as well as Furosemide and Phenazone followed CA-expectations closely in a study by Fent and workers, employing the yeast estrogen screen (Fent, 2006b). Finally, even investigations in multi-species tests show a similar pattern: in tests with sewage sludge bacteria, the toxicity of a binary mixture of the two quinolone antibiotics oxolinic acid and flumequine followed the predictions made by CA (Christensen, 2006), and the effects of a five-compound mixtures of antibiotics followed the CA-prediction in studies with natural planktonic bacterial communities (Brosche, 2010).

Comparatively, only few studies with mixtures of dissimilar medicinal products have been documented in the scientific literature. The results from a 14-compound mixture indicated that the competing concept of Independent Action (IA) provided a good prediction of the experimentally observed toxicity, while CA slightly overestimated to observed mixture toxicity (Backhaus, 2000). An algal toxicity study (with the five dissimilar medicinal products Propranolol, Sulfamethoxazole, Ethinylestradiol (EE2), Diclofenac, Ibuprofen and the herbicide Diuron) resulted in a mixture toxicity that followed IA expectations in the lower tested concentration range and CA in the region of higher

concentrations (Fent, 2006). This was explained by the fact that four of the components (Sulfamethoxazole, EE2, Diclofenac, Ibuprofen) were classified as acting primarily as baseline toxicants in algae and hence sharing an identical mode of action, despite their different chemical classes.

However, medicinal products have a multitude of possible modes of action in different environmental organisms and there is currently a lack of understanding of the toxico-kinetic as well as toxikodynamic interactions between most medicinal products and environmental organisms. Hence a mode-of-action driven selection between CA and IA as "the best" predictive model does not seem feasible now. It might hence be more productive, to base at least an initial assessment on the application of CA only. This, however, is only justifiable, if on average only minor errors are to be expected when the concept is used for mixtures that are not composed entirely of similarly acting compounds. It has been proven that relevant differences between both IA- and CA- predictions may occur only when the mixture contains a considerably large number of mixture components that all have rather steep or flat concentration-response relationships (Kortenkamp, 2009) (Backhaus, 2012) Consequently, in all available studies that comparatively assessed both predictions, only minor differences in terms of EC50-values between the CA- and IA-predicted concentration-response curves have been observed, with CA typically predicting slightly higher toxicities. This argues for the notion that CA might be applied in a first tier risk assessment of medicinal products, which is also in line with e.g. the recent outline for mixture risk assessment for human health as suggested by the WHO (Meek, 2011).

This is further supported by the available empirical evidence, which indicates that mixture toxicities much higher than predicted by CA – i.e. synergisms, which would be most problematic from an environmental risk assessment perspective – occur only rarely. The ratio between CA-predicted and observed effect concentrations (e.g. EC50-values) is usually lower than a factor of five, with the vast majority of studies showing a clearly lower ratio. Taken together, all this implies that especially CA might be a valuable tool for the predictive hazard and risk assessment of pharmaceutical mixtures (Kortenkamp, 2009) (Backhaus, 2012) (Lawrence, 2005).

It should be finally pointed out, that the problem of joint effects from multi-component chemical mixtures in the environment is not restricted to medicinal products only. Typical mixtures in the environment also contain a multitude of chemicals from other regulatory areas, e.g. industrial chemicals, pesticides and biocides. The issue has therefore been analysed from a broader perspective (Kortenkamp, 2009) (SCHER, 2011) and has recently also begun to lead to regulatory action (COM, 2012). The Environment Council of the European Union published its conclusions on the issue of chemical mixtures, with a particular focus on endocrine disrupters on the 22nd of December 2010. This document calls for more research in the area as well as more debate on the legislative aspects concerning this issue, and in particular, how this can be considered in future legislation through the application of the precautionary principle[45].

In view of the complexity of environmental exposures to chemicals, it is hardly surprising that a recent survey by UK NIEHS (Boxall, 2012) identified the question of the relative importance of medicinal products in comparison to other chemicals and non-chemical stressors as the number one open questions with respect to medicinal products in the environment.

45 www.consilium.europa.eu/homepage/showfocus?lang=en&focusID=65453

5.4 Chapter summary

5.4.1 Key messages

Although the scientific assessment of ecotoxic effects of human and veterinary medicinal products on organisms in the environment is still less developed than e.g. for pesticides, it becomes increasingly clear that some medicinal products, in particular anti-parasiticides, anti-mycotics, antibiotics and (xeno)estrogens, pose environmental risks in certain exposure scenarios. For other medicinal products, environmental risks can be rather negligible, due to low environmental persistence and ecotoxicity of the compounds. However, the situation is far from being clear for the majority of medicinal products currently on the European market. This is a consequence of the still insufficient publically available knowledge on the ecotoxicology of many medicinal products, often deduced from few acute ecotoxicity data collected from a very limited number of freshwater species. It should also be pointed out here, that the knowledge on environmental occurrences is equally limited for many medicinal products, making a sound and transparent environmental risk assessment almost impossible in many cases. In order to gain a better understanding of the environmental hazards of medicinal products, their ecotoxicologically relevant modes of action need to be better identified and clearly differentiated from the modes of action that are relevant in a human pharmacological and toxicological context (although, of course, there might be overlaps for certain groups of compounds). In particular, possible effects in an ecological context, i.e. on a super-organism level, warrant more attention.

5.4.2 Knowledge gaps

- Publically available, high quality data on chronic ecotoxicity are still scarce or even absent for a broad range of human and veterinary medicinal products.
- Knowledge on the ecotoxicity of medicinal products to terrestrial and marine organisms is even more limited.
- Data from human toxicology studies might help to read-across to potential effects on environmental vertebrates (e.g. teleost species). Similarly, data on antimicrobial efficacy can be employed for getting a first idea on potential effects on environmental microbes. However, read-across and extrapolation approaches for other medicinal products and/or environmental organisms are largely missing, or might even be impossible due to ecotoxicological modes of action that are not relevant in human studies.
- Possible mixture effects of medicinal products are not considered during the regulatory environmental risk assessment in current EU guideline documents.

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Chapter 6: Human exposure through the environment and possible impacts

6.1 Human exposure through the environment

The detection of low levels of medicinal products in rivers and streams, drinking water, and groundwater has raised questions as to whether these levels may have consequences to human health. Humans are unintentionally exposed to very low concentrations of medicinal products via daily intakes of drinking water, leaf crops, root crops, fishes, dairy products, and meat (Halling-Sørensen, 1998).

Figure 7 shows the most important human exposure routes.

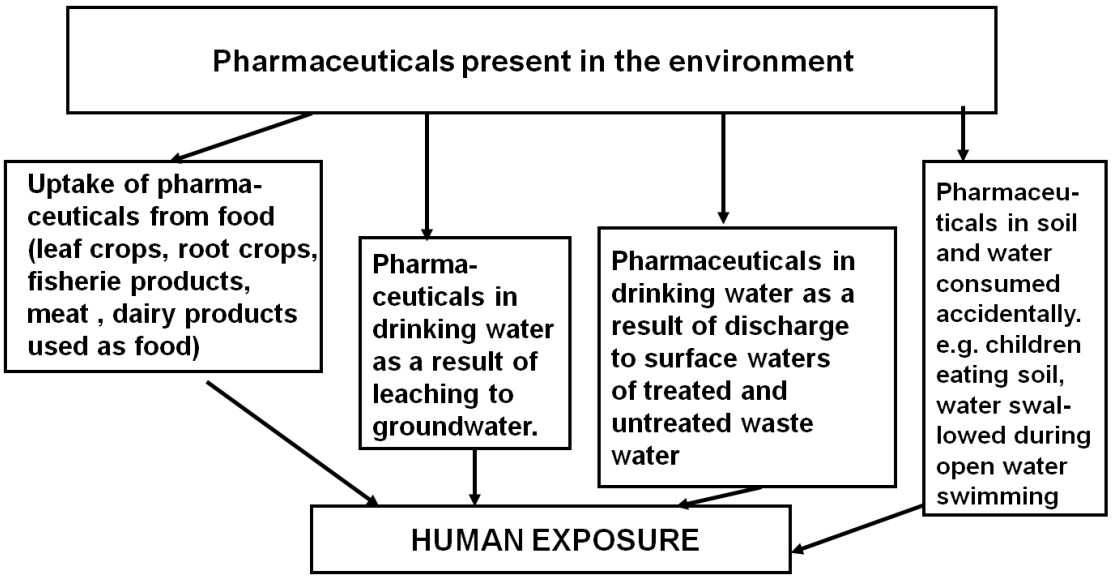


Figure 7: Human exposure routes to medicinal products

Depending on the different use rates of organic fertilisers such as manure or sewage sludge and of treated surface water as drinking water, the potential exposure of humans to medicinal products may vary among EU countries. Organic fertilisers transport medicinal products to food, and medicinal products in surface waters may end up in fish and drinking water.

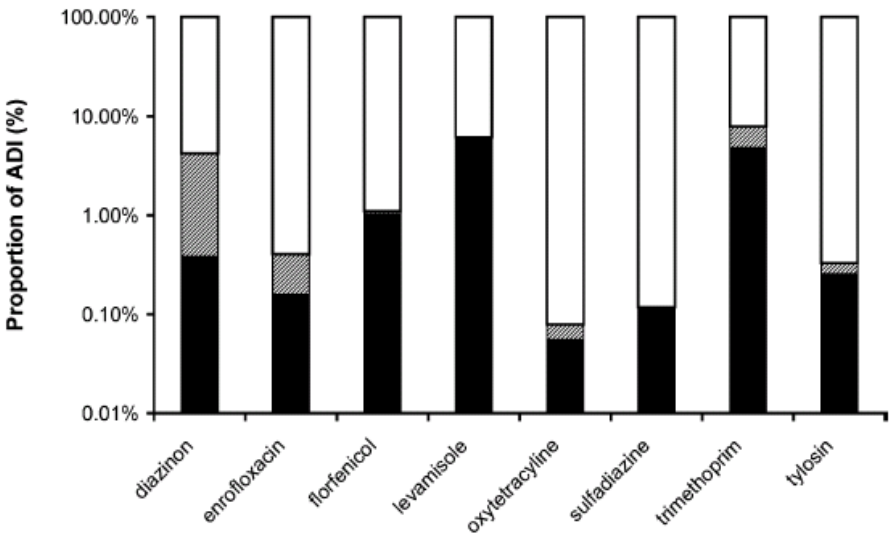
Furthermore, the indirect environmental exposure of antibiotics and medicinal products having anti-bacterial, anti-viral or disinfectant properties may create antimicrobial or anti-viral resistance in human gut flora leading to less effective antibiotics or anti-viral medicinal products in the future. The biggest issue is the transport and spread of resistance around the globe from human to human. If a person from Europe is exposed to an antibiotic compound in a third country, this person will take back the resistance genes in infected bacteria to Europe and be able to spread the bacteria (resistant genes) to other individuals here. Today it may take humans more than 1 year to lose resistance gut bacteria again. Therefore, the possibility to spread them to vulnerable individuals during this period is high. It is important to realise that incorrect application of antibiotics or anti-viral pharmaceuticals

is a global problem that can affect vulnerable individuals many thousands of miles away. A minor exposure pathway might result from recreational activities (e.g. open water swimming, or children eating contaminated soil).

6.1.1 Exposure through the consumption of plant based products

Humans may be exposed to contaminants from sludge or manure through eating crops cultivated on soil where sludge or manure has been applied, if contaminants absorbed in the soil are transferred in plant roots, leaves, etc. The exposure of humans from plant-derived food materials has been estimated using consumption data from a national dietary survey (Norkost, 1997) combined with estimated or measured plant concentrations of medicinal products for different model plants (Boxall, 2008). Boxall and co-workers (2008) studied the potential for a representative range of veterinary medicinal products to be taken up from soil by plants (lettuce and carrots) and to assess the potential significance of this route of exposure.

Comparison of the actual calculated daily intakes for veterinary medicinal products with the corresponding acceptable daily intake (ADIs) (Figure 8) suggests that for the study compounds exposure of consumers to veterinary medicinal products in soils via plants is likely to be considerably below the ADI and that the **direct** risk to human health is thus probably low. The most bioaccumulative compounds (insecticide), Levamisole (insecticide) and Trimethoprim (anti-infective drug) via non-green food only accounted for less than 10% of the ADIs. This simplistic risk assessment is very conservative, because it assumes that all plant material consumed in the diet is derived from crops grown with manure containing veterinary medicinal products. The study has focused exclusively on parent medicinal products and on single-substance exposures. It is likely that many of the study compounds will have degraded in the soil or in the plant into transformation products.



Solid bars represent exposure via non-green vegetables, and hatched bars represent exposure via green vegetables (Boxall, 2008).

Figure 8: Potential contribution of veterinary medicinal products in vegetable material to the acceptable daily intake (ADI)

6.1.2 Exposure through water consumption

Humans may be exposed to contaminants dissolved in drinking water (Schricks, 2010) or adsorbed to particles. As concentration levels of medicinal products in drinking water produced from surface water are generally higher than in drinking water produced from ground water (Debroux, 2012; Stuart, 2012), it can be discussed whether exposure is higher via the drinking water produced from surface sources. Higher levels of concentrations in surface water does not necessarily result in a higher level of human exposure to medicinal products in countries using predominantly surface water, since the actual exposure will mostly depend on the quality of drinking water treatment. The environmental occurrence of medicinal products in surface water have been evaluated and generally found to be low if the waste water is treated before release to the environment, as a large proportion of the contaminants may be removed during filtration processes in drinking water treatment plants.For example, Sanderson (2011) collected data showing trace amounts of medicinal products in surface waters in the nano- to microgram per litre range, but only in the nanogram per litre range and in drinking water. No difference between surface and groundwater sources were reported in terms of human health risks.

The human health risks of trace amounts of medicinal products in drinking water have been evaluated in a report edited by the World Health Organisation (WHO, 2011)[46] as well as in a few countries such as in the UK and the Netherlands (Boxall et al., 2011; Boxall, 2012b; Schricks, 2010; Versteegh, 2007). All reports conclude that, based on available evaluations, the majority of compounds a substantial margin of safety exists between the maximum concentration in drinking water and the concentrations likely to trigger adverse effects, and then that adverse health effects from targeted medicinal products occurring in European water are not expected to individually pose any appreciable risks to human health. However, although preliminary screening level assessments suggest the exposure to be low, they are often based on the use of proxy indicators such as the lowest therapeutic doses as points of departure for the risk assessment (e.g. in Boxall et al., 2011), which does not reflect the specificities of pharmaceutical exposures through drinking water. Therefore, uncertainties remain, in particular with regards to the particularly active nature of the molecule, concerning mixture effects, chronic long-term effects at low doses and sensitive sub-populations. These aspects should be investigated further to verify whether the current exposure leads to a significant risk.

6.1.3 Direct soil ingestion

The calculated concentrations of contaminants (medicinal products) in soil or soil products after sludge or manure application are the basis for assessing the importance of the different routes for exposing medicinal products indirectly to humans in unanticipated ways. It is well known that children may ingest particles at playgrounds that were previously sludge amended. The highest concentrations of contaminants are found on the soil surface due to the use of sludge-containing soil mixtures for private gardens. In an epidemiologic study, 90% of the children ingested less than 0.2 g soil per day (Calabrese, 1989). This amount of soil has been used by several investigations e.g. SFT

[46] analysing risk assessment for drinking water in the UK, the United States and Australia

to establish quality classes for soil in kindergartens and playing grounds for children in Norway (Alexander, 2006).

Halling-Sørensen and co-workers calculated the human health risk for intake of medicinal products via soil (Halling-Sørensen, 2002b). Calculations showed that humans would need to consume 200 g to 1 kg soil in order to be exposed to one adult Daily Defined Dose (DDD) of the medicinal product. The defined daily dose of a medicinal product is the assumed average maintenance dose per day for a pharmaceutical product used for its main indication in adults.

As stated by Alexander (2006) it was anticipated that it was not possible to eat more than 10 grams of soil per day. Thus, it is not possible for either children or adults to be exposed to a whole DDD in one day via soil. On the other hand, it is difficult to establish a "safe level" for medicinal products such as hormones, antibiotics and cancer medicinal products. A "zero tolerance" principle might therefore be proposed and applied to protect vulnerable groups of the human population. However, introduction of such a principle is not easy because management tools have not been developed for avoiding exposure of humans to important pharmaceutical products. Some groups (e.g. children) have for different reasons enhanced sensitivity towards medicinal products such as antibiotics. Humans developing allergies to antibacterial agents or other pharmaceutical products may suffer from being exposed to even very small doses of medicinal products. The evaluation of human health risk for micro-pollutants was based on an exposure scenario where a 10 kg child accidentally ingests 200 mg faeces/day. This dose of faeces will not lead to an exposure level higher than 1/16 of the total daily intake (TDI) for any of the micro-pollutants evaluated.

Contaminated soil ingestion in farmed animals can also be a potential exposure route, even if the current knowledge relates principally to metals (Abrahams, 2003; Waegeneers, 2008). Italian has been working on the relevance of the data to the ingestion of other contaminants, including pharmaceuticals, and their possible appearance in milk and meat, taking account of the concentrations of these contaminants in topsoil amendments including sewage sludge[47].

6.1.4 Exposure through the consumption of meat, dairy and fishery products

Medicinal products can bioaccumulate in cattle anf fish, either through direct exposure for therapeutic purposes (use as growth promoter may still occur but is an illegal practice in the EU) or through the presence of pharmaceutical residues in the environment (e.g. in surface water for fish). Humans can then be exposed to the contaminants through the consumption of meat, dairy and fishery products.

FAO, WHO, the International Office of Epizootics (OIE) and a number of national governments have lately raised the issue of irresponsible use of antibiotics in all production sectors, including fish industries, with particular concern for the potential risks to public health. Many governments around the world have introduced, changed or tightened national regulations related to the use of veterinary medicines, and in particular of antibiotics. In order to protect the health of consumer of foodstuff of animal origin, the EU legislation now foresees that foodstuff obtained from animals

[47] Personnal communication G.Brambilla

treated with veterinary products must not contain residues of the medicine or its metabolite which might constitute a hazard health for the consumer, and Maximum Residue Levels (MRLs) were set in this respect. In Europe, there is therefore a comprehensive control of residues of veterinary pharmaceuticals in products issued from farming and aquaculture, and most production is considered of high quality, not containing antibacterial agents, which are the most used in animals, over the MRL levels. While the level of antibiotic residue is low in most cases, this kind of low and constant exposure can lead to antibiotic resistance in both the animals fed the antibiotics and the humans who consume the food. EU (Eudralex, 2005), CVMP/VICH (EMA, 2013) (EMA, 2011) highlighted that consuming foods containing antibiotics could have a direct effect on an individual's own intestinal bacteria and could contribute directly to the bacteria in the bowel becoming resistant to later antibiotic treatment. The risk for resistance and GI-tract disturbances are among the parameters considered when setting MRLs for antibacterial substances.

However, environmental exposure to medicinal contaminants (human or veterinary) of animals is not considered within the MRL regulation. This pathway of exposure is currently poorly characterised. Additional research into deriving methods for assessing these pathways and better quantifying MRL for all medical products as well is suggested to be initiated.

Furthermore, despite MRLs, uncertainties regarding the exposure of humans through the consumption of food arises from the multiple sources of exposure. The exposure to contaminants through consumption of meat, dairy and fisheryproducts has been estimated using food consumption data from the dietary surveys conducted in different MS. For organic contaminants, the model given in TGD may be used for biotransfer into food products such as meat, milk and fat. However, unfortunately data are scarce so it is difficult at present to perform a complete calculation for any medicinal product (i.e; data characterising the transfer of medicinal products in the food chain). In order to estimate the total daily intake of medicinal products, the content in drinking water and food from all possible exposure routes should be combined. To estimate a total average intake of a contaminant from all sources, the average intakes from the different food groups should be aggregated. At present, this is impossible for medicinal products because existing data do not allow such calculations due to incompleteness of data for most medicinal products.

6.2 Hazard potential of some categories of medicinal products

The human medicinal products recognised as potential environmental and food hazards are primarily medicinal products used in high volumes and medicinal product groups with special properties such as hormones, anticancer medicinal products, pain killers, and antibacterial medicinal products (Halling-Sørensen, 1998) (Jørgensen , 2000). High volumes of human medicinal products include groups such as non-steroid anti-inflammatory medicinal products, beta-blockers and lipid lowering agents.

Hormones are substances involved in cell signalling in humans. They are effective at low concentrations (ng/l level) and as medicinal products; they are used as natural, nature identical and synthetic substances. As contaminants in the ecosystem, hormones have already been shown to disrupt biological signal pathways (Daston, 1997).

Anticancer medicinal products are optimally designed to kill/inhibit malignant tumour cells at doses that allow enough unaffected cells in critical tissues with high cell proliferation rates to survive so that recovery can occur. Different substance groups with specific mechanisms of actions are used in anticancer chemotherapy; however, most are generally genotoxic, mutagenic and reprotoxic already at relatively low concentrations. A few new classes of anti-cancer drugs such as the tyrosine kinase inhibitors and monoclonal antibodies are not genotoxic. An unintended human exposure of anticancer medicinal products via drinking water (which are detected in drinking water) or food could be problematic.

Antibacterial medicinal products are compounds that kill or inhibit the growth of bacteria. Antibacterial medicinal products comprise a fourth group of importance due to their potential for resistance development caused by selection for resistant bacteria. Several studies suggest a link between antibacterial use and antibacterial-resistant infections (Smith, 1999). The development of antibacterial resistance is usually favoured by sub-inhibitory concentrations of these medicinal products. For instance, the numbers of antibacterial resistant microorganisms in samples taken from the outlet of fish farms under treatment and the presence of resistant bacteria treated with pig manure are increased and there is evidence that the antibacterial resistance from agriculture can be transferred to humans (Boxall, 2008).

6.2.1 Antimicrobial resistance (AMR)

The increasing resistance to antimicrobial medicinal products represents one of the major emerging threats to human health. Without any doubt, the development of AMR is by far the largest risk for humans of having medicinal products residues in the environment. AMR is a major European and global societal problem, involving many different sectors e.g. medicine, veterinary medicine, animal husbandry, agriculture, environment and trade. It cannot be successfully tackled through isolated, sectoral efforts. Food and direct contact with animals may serve as a vehicle for the transmission of AMR from animals to humans, emphasising the link between human and veterinary medicine in line with the "One Health" initiative[48].

The fact that resistance may spread from country to country when people and animals travel or when food, feed and other possible vehicles of AMR are traded, stresses the need for coordinated efforts across borders.

To address this, a holistic approach is required in line with the "One Health" initiative. The Commission proposes to put in place a 5-year Action Plan to fight against AMR based on 12 key actions (COM, 2011). The 12 key actions are shown in Box 3. Several MS have been pro-active in carrying out actions related to those considered at EU level. These actions at MS level and the

[48] www.one-health.eu

experience gained from it should be the basis of the practical development and implementation of this Action Plan.

Box 3: EU action plan against the rising threats from Antimicrobial Resistance

Action n° 1: Strengthen the promotion of the appropriate use of antimicrobials in all MS

Action n° 2: Strengthen the regulatory framework on veterinary medicinal products and on medicated feed.

Action n° 3: Introduce recommendations for prudent use in veterinary medicine, including follow-up reports.

Action n° 4: Strengthen infection prevention and control in healthcare settings.

Action n° 5: Introduce a legal tool to enhance prevention and control of infections in animals in the new Animal Health Law.

Action n° 6: Promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antimicrobials to patients.

Action n° 7: Promote efforts to analyse the need for new antibiotics into veterinary medicine

Action n° 8: Develop and/or strengthen multilateral and bilateral commitments for the prevention and control of AMR in all sectors.

Action n° 9: Strengthen surveillance systems on AMR and antimicrobial consumption in human medicine.

Action n° 10: Strengthen surveillance systems on AMR and antimicrobial consumption in animal medicine.

Action n° 11: Reinforce and co-ordinate research efforts.

Action n° 12: Survey and comparative effectiveness research.

6.2.2 Background knowledge for AMR development

It is important to stress that there needs to be a certain minimum concentration of antibacterial drugs present before any effect on bacterial growth is observed and therefore any selection pressure for resistance is present.

The most important location for the development of antibacterial resistance is probably in the gut of humans or animals receiving antibacterial medicinal product therapy. Resistant bacteria and resistance genes that have developed due to presence of antibacterial medicinal products in the gut will be excreted together with the faeces. When that faeces becomes part the wastewater sludge, resistant bacteria and resistance genes may reach arable land if the sludge is used as soil conditioner. Such resistance may be spread further, either vertically or by horizontal spread of genetic elements to other bacteria. A second way, though probably less important than the one described above, is resistant development due to a selection pressure of dissolved antibacterial medicinal product residues in sewage water, and hot-spots (e.g. certain departments in hospitals), typically in the µg/l concentration level. Those residues may exert a selection pressure to bacteria that favours resistance development in the sewage treatment plant (STP). Again, the sludge may contain, as above, genetic elements that can be transferred at a later stage to other bacteria. Finally, a third way that may impose a selection pressure can happen in the soil compartment itself due to antibacterial medicinal product residue molecules (typically in the low µg/kg soil DW). They are transported with sludge to the topsoil and desorb from the waste to the soil compartment.

Theoretically, they can exert a selection pressure to existing soil bacteria, which may develop resistance. These genetic elements may again be transferred to other soil bacteria. This is likely a less important way of inducing resistant elements into the soil compartment.

It is important to realise that there is an abundance of naturally occurring resistant bacteria in the environment even without any prior contact with antibacterial drugs.

As concluded in the Action Plan against the rising threats from Antimicrobial Resistance (COM, 2011), the development of resistance, the pressure to reduce the use of antimicrobials as well as the weak market incentives and increasing difficulty and cost to develop new effective antibiotics, have discouraged investment in this area with the consequence that only a few new antibiotics are currently under development.

Increasing global trade and travel favours the spread of antimicrobial resistance between countries and continents. Therefore, antimicrobial resistance is a global public health concern leading to increased number of suboptimal treatments and treatment failures of bacterial diseases. The emergence and spread of antibacterial resistance are complex processes. They are driven by numerous interconnected factors. Selective pressure from exposure to antibacterial medicinal products, which causes the emergence of resistant bacteria that may become predominant within the population, is considered the most important factor.

Several different mechanisms are involved in the development of resistance to antibacterial medicinal products. The scientific world is still struggling to understand the mechanism of transporting resistance via the environment to humans. Field information related to the spreading of genetic material from biosolids into soil is still very limited. Demoling & Baath (Demoling, 2008) reported that no long-term persistence of bacterial pollution-induced community tolerance was observed in Tylosin-polluted soil. Exposure to antibacterial medicinal products may cause intrinsic processes or mutations in bacterial DNA (e.g. chromosome, plasmid), resulting in reduced susceptibility or resistance to one or more antibacterial medicinal product (Lipsitch, 2002). Furthermore, acquisition of resistance by bacteria through uptake of new genetic elements through horizontal gene transfer coding for resistance is another mechanism (Lipsitch, 2002). Resistance genes may be acquired by uptake of pieces of DNA originating from the chromosome of other bacteria or by acquiring mobile genetic elements such as plasmids or transposons (Davis, 1994). This increases the occurrence of resistance genes associated with transferable genetic elements, and may entail further dissemination of resistance genes to other bacterial species (Lipsitch, 2002). Various studies have reported the presence of multi-resistant bacteria both in untreated and treated sludge (Boczek, 2007) (Ferreira da Silva, 2007).

Box 4 provides some examples of the resistance phenomenon.

Box 4: Examples of the resistance phenomenon

Antibacterial medicinal products can be found with increasing frequency in wastewater and sewage sludge, and in parallel, an increased level and frequency of resistant bacteria in the environment has been observed (Reinthaler, 2003). Combined effects of different antibacterial medicinal products that were higher than predicted based on the assumption of concentration addition were shown.

In a study on the occurrence of *E. coli* in sewage and sludge, it was shown that microorganisms with resistances to antibacterial medicinal products accumulated in the sludge (Reinthaler, 2003). *E. coli* strains

were found which were resistant to 16 out of 24 tested antibacterial medicinal products (penicillins, cephalosporins, aminoglycosides, quinolones, and others); the highest resistance rate (up to 57%) was found for tetracycline.

Although treatment of sludge reduces the number of bacteria, including the resistant ones, it will not entirely eliminate all such bacteria. If inadequately treated sludge is used as fertiliser, agricultural products used as food or animal feed may be contaminated (Ensink, 2007) (Heaton, 2008) (Keraita, 2008) , and such phenomena have been the sources of several outbreaks of enteropathogenic infections (Heaton, 2008).

Proven spread of enteropathogenic pathogens may be regarded as an indication on spread of other enterobacteria (Høiby , 1995) and these may carry resistance genes.

Bacterial DNA that contains resistance genes can be released to soil from microorganisms after treatment of sludge. Bacterial DNA may persist in soils for weeks and months (Picard, 1992) (Recorbet, 1993) (Romanowski, 1991) but the biological activity of DNA released into natural soils has been demonstrated for bacterial DNA for limited periods (Nielsen, 1997).

The stability of DNA in soils is dependent upon several factors like soil type, its composition and pore sizes, temperature, soil moisture, aeration, concentration of in/organic nutrients and salts, pH, bacterial activity and density, extracellular enzymatic activity, and soil interaction with meso-macrofauna and flora (Nielsen, 197b).

The transfer of bacterial DNA to environmental "free-living" bacteria has been demonstrated in several studies, mostly in laboratory models, often by means of an introduction of antibacterial medicinal products in concentration at a much higher level (mg/kg DW soil) than that found in natural soil environments (Nielsen, 1997c) (Nielsen, 2000) (Smalla, 2000).

Transfer to soil bacteria of antibacterial resistance genes from manure used as fertilisation has also been confirmed (Heuer, 2007) (Binh, 2008) , and again this has been demonstrated only at the mg/kg DW manure of an antibacterial medicinal products. The frequency of such transfers depends on several factors like the number of bacterial species capable of transferring genes, factors that regulate their host range, the nature and availability of transferred DNA, the transfer efficiencies, and the selective pressure acting on the bacterial transformation. Sengeløv (2003) reported that resistance to Tetracycline, macrolides and Streptomycin was measured for a period of 8 months in soil bacteria obtained from farmland treated with pig manure slurry. The control soil was not amended with animal manure. The occurrence of tetracycline-resistant bacteria was elevated after spread of pig manure slurry but declined throughout the sampling period to a level corresponding to the control soil. A higher load of pig manure slurry yielded higher occurrence of tetracycline resistance after spreading; however, the Tetracycline resistance declined to normal occurrence defined by the Tetracycline resistance occurrence in the control soil. Results obtained indicate that Tetracycline resistance levels in soil are temporarily influenced by the addition of pig manure slurry and that increased amounts may result in increased levels of resistance for a shorter period.

A second field study in southern Denmark consistently reported that the level of aerobic antibiotic resistant bacteria in the soil over time and soil fauna community was assessed in relation to application of manure containing antibacterial medicinal products to the agricultural fields (Halling-Sorensen, 2005).

The level of both CTC- and TYL-resistant bacteria was affected in the soil by amendment of manure, but declined during the study to the same level as that observed at the beginning.

6.3 Risk analysis

Studies have shown that medicinal products are especially present in water bodies. Due to the observed concentrations, risks are more related to possible cumulative effects of long-term low-dose exposures than to acute health effects (Daughton, 1999).

There is currently a lack of guidance on how the risk assessment for humans of the presence of medicinal products in the environment may be conducted. However, several authors have evaluated the risk of indirect environmental exposure to medicinal products.

Human pharmacology and toxicology data of human Active Pharmaceutical Ingredients have been used for developing acceptable daily intakes (ADIs) which are believed to be without pharmacological, Threshold of Toxicological Concern (TTC) and toxicological effect or minimum therapeutic dose (MTD) which were used as reference exposure concentrations to be compared to the modelled or measured real exposure through the environment. A report edited by the World Health Organisation (WHO, 2011), analysing risk assessment for drinking water in the UK, the United States and Australia, concludes that appreciable adverse health impacts to humans are very unlikely from exposure to the trace concentrations of medicinal products that could potentially be found in drinking water. The findings from these three case studies are in line with the evidence published in other countries. For instance, a study conducted in Germany and data reported in table 2 found that the margin between indirect daily exposure via drinking water and daily therapeutic dose was at least three orders of magnitude, concluding that exposure to medicinal products via drinking water is not a major health concern (Webb, 2003). Previous studies have come to the same conclusion for exposure of medicinal products, such as neuromedicinal products (Bercu, 2008), cytotoxic medicinal products and iodinated contrast media, in water or from fish consumption (Cunningham, 2009).

However, uncertainties and particular concerns still exist. First, in the majority of cases, the targeted population consists of healthy adults exposed through drinking water. Thus, the risk evaluation would need to be specifically normalised applying worst-case scenarios for sub-populations (e.g. children, pregnant women and foetus, allergic people).

Moreover, the real exposure is to a mixture of medicinal products in trace amounts and not only through drinking water. Thus, the total burden of exposure could be better evaluated once more information on food chain transfers could be produced.

Occurrence of multiple medicinal products in water or in combination with other groups of organic or inorganic molecules at low concentrations has been reported in several studies. Consideration of their interactions becomes important, as it constitutes a significant uncertainty. On 31 May 2012, the Commission reported to the Council in its Communication from the Commission on Combination effects of Chemicals (Chemical mixtures) (COM, 2012). In this report, the Commission engaged to launch a new process to ensure that risks associated with chemical mixtures are properly understood and assessed. The report states that EU laws set strict limits for the amounts of particular chemicals allowed in food, water, air, and manufactured products, but that the potentially toxic effects of these chemicals in combination are rarely examined.

Under the new approach, the Commission will identify priority mixtures to be assessed, and ensure that the different strands of EU legislation deliver consistent risk assessments for such priority

mixtures. The Commission will also tackle some of the data and knowledge gaps to improve understanding of the mixtures to which people and the environment are exposed.

A particular focus is suggested to be placed on endocrine disrupters (COM, 2012). These substances act like hormones and disturb the normal functioning of the endocrine system. The endocrine system is a network of glands and hormones that regulate many of the body's functions, including growth, development and maturation. Endocrine disrupters are suspected of interfering with the production and performance of hormones. Such effects have already been seen in animals, impairing reproduction, development or immunity.

Due to lack of understanding about (1) actual composition of pharmaceutical mixtures and (2) toxicity of medicinal products at low concentration levels in mixture with other medicinal products, it becomes difficult to predict bodily responses to these mixtures. On the other hand, it is not possible to evaluate whether mixtures of medicinal products can be more toxic than mixtures of other active organic substances. A mixture of many medicinal products at therapeutic dose is known from the medical world to often create side effects in humans. Kumar and Xagoraraki (2000) used information about Carbamazepine, Meprobamate, and Phenytoin to understand their interaction with each other using a pair of two active pharmaceutical ingredients (APIs) and qualitatively discussed the potential effect of simultaneous presence of different APIs. Although this approach appears to serve the purpose of understanding the interactive effect of APIs, it does not help in getting quantitative risk estimates.

Studies have generally discussed different assumptions following the US EPA guideline for health risk assessment of chemical mixtures. Further, due to the present use of consideration of different uncertainty factors (Ufs) for estimation of HBLs and its subjectivity, the current QPhRA methodology overestimates risk estimates and is expected to compensate for the effect of simplified assumption of no mixture effect on risk estimates.

Due to the potential additive, antagonistic, or synergistic nature of medicinal products, any comprehensive risk assessment method addressing the issue of mixture effects is expected to be complicated. Generally, the additive effect due to different medicinal products is expected if medicinal products act through the same mechanism. In case of different mechanisms Cleuvers and co-workers reported certain mixtures of medicinal products to be higher, even at concentrations at which the single substance showed no or only very slight effects (Cleuvers, 2005) (Cleuver, 2003).Further, these effects could be concentration-dependent as Pomati et al. (2008) observed during their toxicity study using 13 medicinal products. Although most of these studies have assessed toxicity using aquatic indicator species or non-specific tests, findings of these studies provide human health perspectives about effects due to presence of different medicinal products at different levels. So in general, more toxicological work is required to study interactive effects of different medicinal products and other chemicals present in water on different human health relevant endpoints.

6.4 Chapter summary

6.4.1 Key messages

- Antibiotics, anti-parasiticides, anti-mycotics and anti-cancer medicinal products are pharmaceutical groups that are specifically intended to kill their target organisms or target cells and may, via environmental exposure, be the most important compounds affecting human health.
- Chronic low-level exposure to medicinal products exists for the public through drinking water and through residues in leaf crops, root crops, fishery products, dairy products, and meat. Most of these exposure pathways are probably not very important but some pathways, such as dairy products, still need to be fully characterised and the uncertainties below, for example regarding possible long-term effects, should be borne in mind.
- In dairy products produced in Europe, only very low concentrations of veterinary antibiotics are found. Similar results are found for levels of antibiotic residues in drinking water and fish species. For human medicinal products not regulated by a maximum residue level (MRL), information is very sparse on residues with the exception of the presence of residues in drinking water. The levels of residues in drinking water are very low and without concern for humans, as far as can be determined on the basis of current knowledge.
- Countries using surface water for production of drinking water tend to have higher concentrations of pharmaceutical residues in their drinking water than countries only using ground water, because the latter may be less directly exposed to medicinal products.
- To date there are no short-term effects observed on humans. However, the risks of long-term exposure of active pharmaceutical ingredients remain poorly understood. Long-term effects cannot be ruled out with current knowledge, especially with regard to vulnerable humans.
- It seems that there is a stabilised problem with fish imported for food from certain countries outside Europe and containing antibacterial agents exceeding the MRL levels applied in Europe, the US and Australia.
- There is growing concern that combined exposure (mixtures) to chemicals from different sources used for example in agriculture and industry may have adverse effects on human health, even if each individual substance is below its own risk limit. Experts regard the predominant chemical-by-chemical approach in risk assessment as insufficient to protect against the risks of combination effects. Medicinal products including antibacterial agents are often part of the chemical mixture to which humans are exposed. A few medicinal products such as selective serotonin reuptake inhibitors (SSRI) and some anti-cancer agents possess side effects affecting endocrine disruptive activity.

- The development of antimicrobial resistance (AMR) created by antibacterial agents is a global problem and presents one of the major emerging threats to human health today. Current knowledge of solutions to minimise the risks of AMR remains incomplete. In November 2012, the EU presented an action plan against the rising threats from AMR based on 12 key actions.

6.4.2 Knowledge gaps

- Generally, there is a lack of data showing mixture effects of medicinal products by themselves and in combination with other relevant organic pollutants e.g. endocrine disruptors. Under a new approach, the Commission will identify priority mixtures to be assessed, and ensure that the different strands of EU legislation deliver consistent risk assessments for such priority mixtures. The Commission will also tackle some of the data and knowledge gaps to improve understanding of the mixtures to which people and the environment are exposed. Such future action is important to get an overview of the impact of human exposure on medicinal products.
- Experts regard the predominant chemical-by-chemical approach in risk assessment as insufficient to protect against the risks of combination effects (mixtures). The conclusions therefore call for more research in the area, especially in mixtures involving participation of endocrine disruptors.
- Future research investigations should target data collection from vulnerable human groups. The possible additive or synergistic effects of mixtures would be beneficial for an accurate exposure assessment to determine whether there are any potential risks to human health.
- Even though quite a lot of data exist on levels of medicinal products in drinking water, studies should be carried out for providing standardised sampling and analysis protocols to support monitoring studies.
- As such, future research looking into cost-effective methods to prioritise medicinal products within the context of an overall risk assessment will benefit our appreciation of low levels of medicinal products in drinking water from a human health perspective. Research initiatives should focus on the current lack of guidance on how to perform the risk assessment for humans. Methods should be developed for calculating safe levels of non-antibacterial agent medicinal products while including specific vulnerable groups. Furthermore the derivation ofcost-effective methods to prioritise medicinal products will benefit of a better appreciation of the impacts of low levels human exposure trough drinking water.
- Implement the research initiatives launched in November 2012 by the EU presenting an action against the rising threats from AMR based on 12 key actions.

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Chapter 7: Non legislative factors of influence

Non-legislative factors of influence may contribute to the presence of medicinal products in the environment and the associated impacts, including practices along the life cycle, communication issues regarding the possible impacts of medicinal products on human health and the environment, and scientific knowledge gaps of various natures.

7.1 Sustainable production

R&D and manufacturing of medicinal products is a key stage, where are defined the properties of the molecules later placed on the market. In addition to the mode of action and efficiency for target organisms, these properties include characteristics relevant to the occurrence and possible impacts on the environment, e.g. persistence in environmental compartments, bioaccumulation and ecotoxicity/toxicity of original, metabolised and/or transformation products for non-target organisms.

Pharmaceutical industry works towards the development of human and veterinary medicinal products that are the most efficient possible in detecting, preventing and/or treating diseases while minimising side effects for target and non-target organisms. As highlighted by the European Federation of Pharmaceutical industries (EFPIA), research and development strategies are focussed on efficacy, safety and quality[49].

It is often argued that developing greener medicinal products[50] (Kümmerer, 2010) (i.e. efficient medicinal products with a more environmentally-friendly profile compared to conventional medicinal products) raises great technical and economic challenges in addition to timing concerns, which would explain why this option is much less considered by the industry, at least in the short-term. The concept of "green design" adds complexity to the standard process and reduces the number of candidates with satisfactory properties from a therapeutic point of view. The currently available predictive tools may not be good enough yet to be used for developing greener molecules in early medicinal product development. Moreover, the current pharmacology model impedes even more green design initiatives, in particular because of the increased externalisation of research and the increased pressure to find new candidates (Snape, 2012).

Furthermore, the marketing of "green medicinal products" is not yet a demand from EU consumers[49], who also might not be ready to support associated costs. In the EU, there are not any regulatory incentives to develop active substances with greener characteristics either (Kümmerer, 2010).

[49] Based on an interview with EFPIA conducted by BIOIS for the present study.
[50] Green pharmacy has been defined as "the design of pharmaceutical products and processes that eliminate or reduce the use and generation of hazardous substances along the whole life cycle" (EEA, 2010).

Because of these difficulties, pharmaceutical industries rather promote the concept of "green chemistry"[51] (Anastas, 1998), which may include green design but mostly consists in developing sustainable manufacturing practices, with limited emissions, without modifying the formulation of medicinal products. Anastas & Warner (Anastas, 1998) highlights the 12 green chemistry principles. Good Manufacturing Practices (GMP) requires containment measures for few high-risk medicinal products (including cytotoxic medicinal products)[52]. However, for the large majority of medicinal products, green chemistry remains a voluntary practice.

7.2 Tackling overconsumption

Although disease pressures can differ from a country to another, it is very unlikely that the different "needs for medication" explain in themselves neither the high consumption of medicinal products nor the variations observed in the EU. Beyond the need for medication, consumption levels of medicinal products can be explained by increased access to medication (e.g. availability of supply, over-the-counter sales and price); cultural acceptance of medication; relationships between consumers, pharmacists, and doctors; and stimulation of consumption (e.g. marketing strategies, reimbursement schemes). As part of its activities of surveillance, ESAC set up a database on socio-economic determinants related to antibiotic use, including diverse categories of variables related to burden of disease, culture and perception of illness, demographic factors, education and knowledge, healthcare system and socio-economic factors[53].

Although the use of medicinal products to meet needs for medication is hardly questionable, inappropriate and excessive consumption might be at the origin of unnecessary emissions. The concept of "overconsumption", i.e. consumption beyond actual needs (Ordre National des Médecins, 2012), is an easy grasp but it is difficult to assess the scale of this phenomenon in practice, given the subjectivity of what is "needed". Through consultations and prescriptions, doctors are competent for assessing these needs for each patient. However, in practice, a number of medical habits, the OTC status and socio-economic factors might favour the overconsumption of medicinal products.

7.2.1 Overconsumption in the context of OTCs or medicinal products under prescriptions

In the EU, over–the-counter medication is readily available, relatively inexpensive and can be obtained without professional advice that would be based on consumers' needs or history of consumption. It is common for people to self-medicate when having mild pain and headaches,

[51] In pharmaceutical industries, "green chemistry" involves safer and cleaner processes without considering the properties of the final products and "green pharmacy" that aims to generate more biodegradable and more environmental-friendly substances (Kümmerer, 2010).
[52] Based on information provided by a AEMPS (Agencia Española de Medicamentos y Productos Sanitarios in Spain) representative in the questionnaires elaborated by BIOIS in the context of the stakeholders' consultation for the present study
[53] www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50205

colds and allergy symptoms, and gastro-intestinal upset, although these practices importantly vary from a country to another. Some medicinal products can be sold over the counter in some countries with or without the supervision of a pharmacist[54], whereas a prescription would be needed elsewhere (Kümmerer, 2009) (EEA, 2010) (Académie Nationale de Pharmacie, 2008).

OTC medicinal products may then represent a considerable share of the total quantity of medicinal products used (NRDC, 2009) and favour over-consumption (Roig, 2010). For example, OTC-Ibuprofen or Paracetamol are likely to represent a higher share than prescribed ones. Sales of OTC medicinal products are however difficult to estimate since they are not systematically recorded: consumption data from Germany, Poland, Spain and the UK (England and Wales) do not include OTC-medicinal products, whereas detailed data exist in France (KNAPPE, 2008). For example, French consumption of Paracetamol including OTC sales amounts to about 47.1 g per capita per year whereas figures are significantly lower in Germany, Spain and UK, where consumption figures amount to about 4.5, 3.6 and 15.7 g respectively (Roig, 2010).

Prescriptions can contribute to control the delivery of medicinal products with significant and potentially hazardous effects, such as antibiotics, antidepressants and hormones. Over-prescribing has however been reported in a number of MS. For example, a survey of general practitioners in the UK found that more than 80 percent of practitioners self-reported over-prescribing anti-depressants to their patients[55]. In France, 30% to 70% of medicinal products delivered under prescriptions could have been prescribed in excess (IGAS, 2005).

Reimbursement schemes of medicinal products are an essential part of health care systems, which do not necessarily increase the consumption of medicinal products (Madsen, 2009). However, undesirable side effects can occur when a medicinal product loses its reimbursement status. Kanavos (2001) showed that its prescription sales often fall, since doctors may replace it with cheaper alternatives in order to reduce the costs paid by patients. Industries may consequently try to have it reclassified as an OTC medicinal product in the case of prescription-only medicine, so that consumer could buy it on their own. However, industry would then need to assure the authorities that the medicine to be reclassified is safe to be sold over the counter without professional input. The opportunity for self-medication could then increase consumption, following the mechanisms described above.

Beyond the actual need for medication, demand for medicinal products can be stimulated through marketing strategies. Because innovation has been losing momentum in the last ten years, because market authorisations are increasingly controlled and because of increasing competition from generics, pharmaceutical industries tend to invest increasingly in marketing activities (Ordre National des Médecins, 2012). Physicians and patients are confronted every day to advertisements for medicinal products, tailored to sub-populations, seasonal diseases and discomfort. Direct marketing through flyers, ads on TVs or newspapers and in-store marketing are part of marketing strategies of pharmaceutical companies. In the European Union (EU), advertising of prescription-only medicines directly to patients and consumers is forbidden by law. However, advertising may still occur towards professionals through tactical sponsorship, direct mail, convention or hospital displays and service items such as educational films, medical

[54] In the UK and in France for instance, some OTC products are only available in pharmacies.
[55] BBC communication cited in (NRDC, 2009)

illustrations and photographs (Khosla, 2011). By raising awareness of physicians and patients for medicinal products, these practices are likely to stimulate consumption through prescriptions[56] or self-medication. As patients pay for an increasing share of their health care costs and tend to buy product brands they trust (Rönnlund, 2010), they are increasingly targeted by marketing strategies. Marketing towards insurance companies also contribute to promoting new medicinal products e.g. through their inclusion in reimbursement schemes.

It is interesting to note that the EU pharmaceutical sector experienced an increase in marketing and sales expenses over the past decades. These activities have become a major cost item in the expenditures of pharmaceutical industries (ECORYS, 2009). This is in line with practices observed in the US[57].

7.2.2 Unused medicinal products

This section is based on studies focused on human medicines. Causes of unused veterinary medicinal products are similar from a qualitative perspective, but not enough data is available.

Treatment interruptions provide a first explanation of this phenomenon, resulting from a change due to intolerance to the initial medicine (side effects), from voluntary discontinuation[58] and to a least extent from death of patient (Académie Nationale de Pharmacie, 2008). In this latter case, the apparent over-supply is largely unavoidable[59]. In England for example, Bound and Voulvoulis (2005) showed that less than 53% of patients completed their treatment. Over-prescribing and easy access to medicinal products are also possible factors: IGAS (2005) showed that part of the medicinal products distributed and left over in France was due to over-prescriptions; while a study from the US showed that overall OTC medicinal products are likely to go more unused than prescribed ones[60]. The relative influence of each of these factors would gain in being better characterised.

Another reason underlying the generation of unused medicinal products is the difficulty in the current system to tailor the delivery of medicinal products to each patient's needs. Following the industrialisation of the pharmaceutical sector, the size of medicinal products packages (Gauthier, 2011) is increasingly standardised, with fixed volumes or number of pills. This may result in extra-delivery, with medicinal products surplus being generally kept at home, "in case", until they are outdated and must be discarded. The adjustment of medication, in particular for some specific population groups such as children, the elderly and for some severe illnesses such as cancer and transplants, is now increasingly promoted in health strategy (Gauthier, 2011).

Significant shares of unused medicines detained by individuals and pharmacies could be avoided. A UK study showed that this avoidable share may account for approximately 50% of unused

[56] As a result of marketing strategies, physicians can prescribe new, higher cost medications when generics or lower priced brand drugs are available.
[57] In 2008, a new study by two York University researchers, based on 2004 IMS health data estimated the US pharmaceutical industry spends almost twice as much on promotion as it does on research and development, contrary to the industry's claim (Gagnon 2008)
[58] In the UK, a study (YHEC, 2010) revealed that in many instances, unused medicines were those prescribed for short-term or intermittent disorders, with a discontinuation of treatments after the disappearance of symptoms.
[59] For instance, in the UK, over 60 per cent of strong analgesic and approaching 80 per cent of wound dressing returns were reportedly because of patient death (YHEC, 2010).
[60] Data from an unused medication collection program in California also suggested that 52 percent of over-the-counter (OTC) pharmaceuticals are discarded unused, compared to 45 percent of prescription pharmaceuticals.

medicines detained by individuals and between 50 to 70% of those returned to pharmacies (YHEC, 2010).

7.2.3 Strategies for administering pharmaceuticals

Compared with targeted therapies, prophylactic and empiric administration of human and veterinary medicinal products may favour over-consumption of medicinal products (KNAPPE, 2008). No specific data could be found in the EU, but globally, Bowler (2005) showed that the increasing prevalence of MRSA (methicillin-resistant *Staphylococcus aureus*) drives changes to empirical and prophylactic regimens in favour of much greater use of glycopeptides. Calculations made in a hospital suggested that this shift in therapy would increase the total antibiotic budget by 100% (WHO, 2005).

Prophylactic use of veterinary medicinal products has been particularly developed in aquaculture, notably antibiotics, to forestall bacterial infections resulting from the high density of fishes, the difficulty in isolating sick animals and the absence of sanitary barriers (Naylor, 2005). Significant emissions of medicinal products were detected e.g. in salmon and shrimps farming in Norway (Grave, 1999). Antibiotics, in addition to be at the origin of bacterial resistance (see section 6.2.1) are often designed to be persistent in the environment, to ensure that they remain stable in the aquatic compartment, exerting their selective pressure for long periods (EMA, 2010).

The mode of administration (e.g. bolus, injection, dermal) and precautionary practices during administration, may also influence the emissions in the environment. For humans, the external application of veterinary or human medicinal products through ointments or patches for example might favour unnecessary emissions, through the release of medicinal product surplus in the environment, while injections and bolus limit the direct environmental contamination by favouring the uptake by the organisms. Injections however have the inconvenience to leave sharp medical waste after use.

7.3 Effectiveness of the waste management practices

7.3.1 Collection schemes for unused medicinal products and awareness raising

Take-back schemes usually concern only medicinal products for human use, and not non-used or expired veterinary medicinal products, which are usually collected together with other type of veterinary waste or directly disposed of in municipal waste stream[61].

[61] The French authorities indicated that in the case of veterinary medicinal products, the circuit is less formalised than with human pharmaceuticals, and includes veterinarians and professional livestock farmers. Information provided by the French authorities in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.

In the case of human medicines, the absence of collection schemes for human medicinal products in certain countries[62] (Académie Nationale de Pharmacie, 2008) (Niquille, 2008) does not fully explain the low performance in collecting unused medicinal products at EU level (see section 3.3.1).

Collection schemes had been established in 20 European countries in 2009[63] (Académie Nationale de Pharmacie, 2008), including Sweden in 1970 with Apoteket (APOTETEK, 2006), France with the Cyclamed Program[64] (1993), Portugal with the Valormed Program[65] (2001), Spain with the SIGRE system (EEA, 2010) (2003) or Hungary with RECYCLOMED[66] (2005). However, there is no harmonised take back system imposed at EU level. As a result, take back schemes are uneven from one MS to another.

Gaps in collection statistics can be explained by:

- heterogeneity of collection coordination in MS, which might be:
  - at MS, regional (e.g. agreement between the federation of pharmacies and the region in Belgium), local level (e.g. take back and disposal of medicinal products are funded and coordinated by cities in the Netherlands);and
  - managed by government-owned companies (e.g. Apoteket AB in Sweden), environmental non-profit organisation (e.g. SIGRE in Spain[67] and CYCLAMED in France) initiated and/or funded by the industry or industrial stakeholders (e.g. Valormed in Portugal, former VFW/Remedica in Germany[68])[69].
- heterogeneity in implementation of collection schemes by pharmacists: there is no harmonised EU legal obligation and the participation is on a voluntary base in most MS (EEA, 2010) (Roig, 2010).
- lack of awareness of consumers, probably due to insufficient communication (i.e. advertising collection schemes, labelling) despite user-friendly websites[70] and communication campaigns. The latter are generally intermittent, with a limited efficiency[71].

[62] For instance in Germany, the existing take-back scheme was abandoned in 2009, because of an amendment to a German law62, and there is no take-back scheme in The Netherlands. In this latter case, most unused medicinal products are returned to pharmacies disposed of via the collection system for household chemicals or as common household waste, in which case it will be incinerated (as it is prohibited to dispose of domestic waste in landfills). Source: Based on information provided by a representative from RIVM , in a questionnaire elaborated by BIOIS in the context of the stakeholders' consultation for the present study.
[63] Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Lithuania, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden, United Kingdom.
[64] www.cyclamed.org
[65] www.valormed.pt
[66] www.recyclomed.hu
[67] Funded by the pharmaceutical industry and operational in 20000 pharmacies in Spain.
[68] VFW / Remedica gathered 320 industrials and proposed a free take-back service to 15 500 pharmacies. It was abandoned in June 2009 following a national law on packaging, which recommended discarding pharmaceuticals directly into municipal waste.
[69] Information collected from: www.cyclamed.org/circuit/etranger
[70] For instance, website of SIGRE initiative: www.memoriasigre.es/2011/
[71] Based on an interview with EFPIA conducted by BIOIS for the present study.

- insufficient structuring of the sector in the case of veterinary medicinal products, where the collection of unused medicines remains more informal and is mostly organised by veterinaries and professional breeders.
- much fewer information is available for the collection schemes and relative efficiency of unused veterinary medicinal products, which are mostly collected with household waste or which can be disposed of directly by the vet[72].

7.3.2 Containment of run-off in farms and urban areas

Run-off water from farms or impervious urban areas can be contaminated by large quantities of pollutants, including medicinal products (Sinclair, 2007). Farms or urban areas are not necessarily designed to contain run-off. Hence, wastewater is not always discharged into the sewage network and can end up infiltrating the soil and the groundwater, leading to environmental contamination.

A number of best practices allow mitigating this issue. For instance, farmers must comply with the post-treatment withdrawal periods specified on the product labelling. In compliance with Article 11 of Directive 2009/128/EC on sustainable use of pesticides, all MS shall also ensure to put in place appropriate measures to protect aquatic environment and drinking water, including measures to minimise the risk of off-site pollution caused by run-off. At farm level, those measures reducing run-off water can positively contain such potential source of medicinal contamination.

7.3.3 Inefficiencies of treatment/elimination processes

As pinpointed in section 3.3 the waste treatment of medicinal products is not always optimal or adapted due to some shortcomings existence in the efficiency of current disposal processes.

Wastewater treatments

Current municipal sewage treatment plants cannot guarantee a complete elimination of medicinal products (Miege, 2009) (Reemtsma, 2006) (KNAPPE, 2008). Efficiency of treatment mainly depends on:

- type of treatment technologies chosen which allows eliminating (degradation) or removing active pharmaceutical ingredients to a certain extent (See Box 5) (biological technologies: conventional activated sludge, membrane bio reactor, bio film systems; separation technologies: nano-filtration, reverse osmosis, activated carbon, sand filtration; or oxidative technologies: ozonation, ultra violet light and hydrogen peroxide (UV/H_2O_2).
- nature of the substances to be treated, which influences the degradation or sorption rate: polar compounds are mainly eliminated in biological treatment, while hydrophobic compounds are rather removed through adsorption on

[72] www.wastebook.org/clinical.htm

sewage sludge (Carballa, 2003). Treatment cannot be calibrated for each therapeutic group since even within the same group, degradation rates would not be the same depending on the specific chemical structures of the molecules treated.

- high concentration of medicinal products in sewage. This can be because there is no pre-treatment of effluents from hospital or farms, where large quantities of pollutants are generated, before their discharge in municipal sewage. In this context, the Netherlands and Germany tested the collection and treatment of wastewater from hospital before their discharge in municipal networks, which appeared to give significant results (KNAPPE, 2008).

Box 5: Efficiency of various treatment technologies

As treatment must take place at existing facilities with very different processes and capacity to remove medicinal products today, the methods needs to be tailor-made to almost each individual plant or group of plants with similar process schemes. Each technology has its advantages and shortcomings; the latter including the production of non-wanted transformation products, increased sludge handling, and increased use of chemicals and costs associated with implementation (EEA, 2010).

Amongst advanced technologies, ozonation and activated carbon show the most promising results. The efficiency of these treatments depends mainly on the treatment capacities (e.g. 0.125-0.5 m^3/h for ozonation compared to 0.1 m^3/h for UV/H_2O_2) as well as sludge and hydraulic retention times (e.g. 0.5 h for ozonation compared to 1.8 h for UV/H_2O_2). In 2003, POSEIDON project showed that the ozonation technology performed effective oxidation/degradation of three major endocrine disrupters (17a-ethinylestradiol, 17b-estradiol and estrone). It was then predicted that ozonation would drastically reduce estrogenic effects on fish caused by discharging treated municipal wastewater into rivers and streams. It could also be predicted that the potential for the formation of resistant bacterial strains would be lowered significantly because antibiotics were no longer detected in the ozonated wastewater (Carballa, 2003). In line with these results, a Swedish study showed that additional treatment with active carbon or low dose ozone (5 mg/l) would decrease the risk of detrimental ecotoxicological effects in the receiving waters of Henriksdal treatment plant (Björlenius , 2012). These results are also in line with those of two pilot trials supported by the FOEN in Switzerland[73] which showed that a broad spectrum of organic trace substances could be eliminated (>80%) with ozonation and activated carbon.

Additional treatments are expensive compared with present technologies and require more energy, whereas in some cases, a simple sand filtration may present a good cost-benefit ratio in removing e.g. toxic and endocrine disrupting effects in cases of low dilution of effluent (Stalter, 2010). The same Swedish study shows that additional treatment for APIs would require + 0.1-0.3 kWh/m^3 of energy. The estimation of additional costs widely varies between studies. They are hardly comparable since they very much depend on the initial infrastructure, type of treatment, MS conditions, etc. In the frame of MistraPharma project, it was estimated that introducing an extra step in the purification process of water in Sweden would increase the cost for treatment of wastewater by 10–100 % (Ruden, 2009). According to the aforementioned Swedish study, total costs (investment, running and capital costs) for additional treatment under Swedish conditions would range from 0.1 – 0.7€/m^3. The Swiss study estimates additional costs between 5-10% compared to existing conventional treatment, which would correspond to 15 to 24 Swiss Francs per inhabitant per year.

[73] www.bafu.admin.ch/gewaesserschutz/03716/11218/11223/index.html?lang=en

Moreover, sewage leakages and overflows due to extreme climatic events (storms) or insufficient treatment capacity may impede the efficient treatment of wastewater before its discharge in the environment.

- **Incineration and land-filling**

Medical waste are in principle collected by the dedicatedcollection schemes established in most MS. If this is not the case, solid waste contaminated by medicinal products is generally disposed of with municipal waste, since most medicinal products are not considered hazardous waste (except cytotoxic and cytostatic drugs[74]). Two options are possible: incineration and landfilling.

Both options have their shortcomings in the elimination of medicinal products, as highlighted in section 3.3 when describing the contamination pathways. For example, although incineration is increasingly promoted to eliminate medicinal products residues contained in contaminated waste, the relevance of international guidelines regarding the incineration of hazardous medicinal products is still debated, in particular in terms of temperature of incineration. For example, WHO guidelines suggest the incineration of anti-cancer medicinal products beyond 1 000 °C to 1 200 °C. Some tests contest these temperatures, by showing that almost the totality of anticancer APIs contaminating municipal waste can be eliminated through their incineration at 850°C for 2.2 seconds (Bisson, 1996). Other tests show that incineration of anti-cancer medicinal products do not modify mutagenic and genotoxic properties of the incineration residues (ADEME, 2004).

7.3.4 Valorisation of sludge and manure

The agricultural valorisation of sludge and manure, which may contain human and veterinary products, through land application as fertiliser is increasingly observed in MS[75]. As in the case of Finland, this could be due to the increase in manure production along with the increasing size of dairy cattle farms (Uusi-Kämppä, 2008). Land application of manure and/or sludge is a widespread practice since nearly 100% biosolids are reused in Finland and more than 87% in Luxembourg, Cyprus and Portugal[75]. These practices favour the release of medicinal products in the soil and their leaching to groundwater later on, since, as shown in section 3.3, medicinal products can be present in significant concentrations in farm animal excretions and sewage sludge. Composting however allows reducing the concentrations on medicinal products.

7.4 Awareness of potential impacts of medicinal products

Practices described above show that the possible impacts for human health and the environment of the presence of medicinal products in the environment are perceived differently depending on countries and on stakeholders.

[74] Nomenclature in Commission Decision 2000/532/EC, n° 18 01 08, 18 02 07 and 20 01 31.
[75] Interview with Bent Halling Sorensen, in the context of the experts' consultation carried out by BIO for the persent study.

The low level of general public's and health professions' awareness of environmental impacts of medicinal products is mostly due to the difficulty to appreciate these impacts and to communicate on this issue. Although representatives of the health sector often acknowledge possible impacts of medicinal products on the environment[76], these possible impacts are not necessarily considered in light of the benefits of medicinal products for human and/or animal health. Environmentalists rather invoke the precautionary principle to pay more attention to the issue of medicinal products, in particular in third countries and in view of future medication challenges posed by increasing and aging population. These different perspectives significantly influence the efforts of the research community to understand possible risks posed by medicinal products and the willingness of stakeholders in developing concrete preventive/mitigation/remediation actions.

A number of operational levels for communication have been identified, targeting different group of stakeholders and comprising EU and government authorities, pharmaceutical producers, doctors, veterinary and other health-care professionals, pharmacological committees, patients and water authorities (EEA, 2010). The success of initiatives such as Cyclamed in France or the environmental classification of medicinal products in Sweden, which both required the collaboration of various stakeholders, show that overall communication could be improved to achieve a better awareness of actual and possible issues related to medicinal products. The classification of medicinal products was developed in Sweden through a joint initiative of the Stockholm County Council, the state-owned pharmacy chain Apoteket and the Swedish Pharmaceutical Industry Association. This classification and especially the editing of corresponding booklet aimed at helping professionals responsible for prescriptions select the most environment friendly treatment amongst treatments of similar efficiency.

Overall, awareness-raising campaign had also proven to be efficient, e.g. to improve collection of unused medicinal products provided they are sustained and target various stakeholders (see section 7.3.1).

Possible environmental effects of medicinal products still seem underestimated during future doctors' education and training. For example, in France, formation about environmental effects in pharmacology would be negligible during doctors' studies and doctors, who would be informed on specific medicinal products later on and throughout their career by industrial-related counsellors (Ordre National des Médecins, 2012).

[76] Based on the analysis of stakeholders' replies to questionnaires elaborated by BIOIS for the present study and following stakeholders' comments during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012.

7.5 Lack of Knowledge

7.5.1 Monitoring strategies, analytical methods and indicators to measure the presence of medicinal products in the environment

Although monitoring strategies and analytical methods have been remarkably improved in the last ten years, the detection of medicinal products in the environment can be limited by the:

- **heterogeneity in the selection of substances targeted**. Because of their significant number, not all the medicinal products, metabolites and transformation products possibly released into the environment can be monitored and choices need to be made based on prioritisation strategies. Several strategies of prioritisation exist, based on hazard or exposure approach, which have been applied differently depending on countries, in Europe and elsewhere[77]. What approaches should be used to prioritise PPCPs for research on environmental and human health exposure and effects is still one if the Top 20 questions raised during the NIEHS' international consultation (Boxall, 2012). According to one of the academic participants, the fact that the pharmaceutical sector, which detains the most accurate information on the types of substances and quantities produced throughout the year, is not necessarily associated to the choice of substances to be monitored may significantly limit its relevance[78]. To date there is no systematic coordination of the prioritisation approaches for medicinal products monitoring at the European level[79] substances being monitored when judged necessary by stakeholders[80]. An exception at the EU level concerns the Water Framework Directive, which proposed to include three medicinal products in its priority list (as mentioned in section 8.3.5), which would involve their mandatory monitoring.
- **difficulty in monitoring certain compartments**: extensive monitoring exists for surface water, groundwater, drinking water, and sewage but very few data exist on soils, sludge and sediments (see Chapter 4 Which molecules are found in the environment and how do they behave?). Beyond the lack of adapted methods (see below), the main reason for little monitoring in these compartments pointed out by two academic interviewees[77] is that, unlike water, the risk of exposure is often considered negligible, since possibilities of direct intake are limited. However, sludge could be contaminated through the adsorption of molecules in wastewater treatment infrastructures, sorption being the main removal

[77] Interview with Prof. Alistair Boxall from the University of York. Information confirmed by existing literature, e.g. in France with the work of Besse et al. (2008), which establishes a preliminary classification based on the assessment of exposure; in the US with the work of US EPA (ToxServices LLC, 2008)
[78] Information based on the interview with Dr. Bryan Brooks for the present study.
[79] As highlighted by the UBA representative during an interview and confirmed by NIEHS.
[80] Based on an interview with EFPIA conducted by BIOIS for the present study.

mechanisms (KNAPPE, 2008); **and may be at the origin for bioaccumulation in the food chain,** when re-used for agricultural purposes.

- **heterogeneity of sampling protocols:** depending on the choice of location, and the number of samples, etc., monitoring data can be more or less representative of the actual presence of medicinal products in the environment. Although monitoring is now carried out on a regular basis, with much improved techniques, the reliability of the data obtained can still be questioned[78].
- low environmental concentrations of medicinal products which can be below standard detection levels and do not allow quantification.
- cost of monitoring campaigns.

It also has to be noted that the indicators routinely used to monitor water quality in hospitals or manufacturing outlets (e.g. organic matter, concentration in oxygen) do not generally consider specific contamination by medicinal products.

Furthermore, monitoring of pharmaceutical contamination generally does not permit determining:

- the origins of emissions, e.g. from hospitals vs. households: some medicinal products can be used in both environments and excretions are released through common sewage networks. Even in cases where emissions from hospitals could be distinguished from those from households, the increase in ambulatory treatment would make it difficult to attribute emissions to hospital or household medication.
- the stage of the life cycle at which they were released: due to the different registration situations in various countries, with deviating and/or overlapping use in human and veterinary medicine, no pharmaceutical compounds are in general fully attributable to veterinary purposes only (KNAPPE, 2008).

7.5.2 Limitations in hazard and risk assessment approaches

Concerns have been raised over whether traditional indicators (e.g. survival, growth, reproduction) can or not:

- reflect the multiple and complex possible modes of action of medicinal products (genetic, molecular, etc.). In this context, the experience from risk assessment of other plant protection products or biocides, which are "designed substances with specific mode of action", shows that far from all effects in biota may be predicted from the mode of action (see section 5.1);
- identify subtle non-lethal and ecologically important effects of a chronic exposure of target as well as non-target organisms (Brooks, 2005) (Kümmerer, 2009) (KNAPPE, 2008).

In other words, some researchers conveyed serious concerns about whether standard tests and endpoints (notably described in the risk assessment guidelines – Section 8.1.2) allow looking at the right responses in the right organisms[81] following chronic exposure to medicinal products. The effect of the non-steroidal anti-inflammatory compound, Diclofenac, on vulture populations (Oakes, 2004) provides an illustration of an endpoint that would not have been predicted from standard studies, because chronic toxicity from long-term exposure would not be considered. Same concerns exist for antibiotics and anti-cancerous medication.

In this context, the relevance of the PNEC/PEC ratio used to characterise the environmental risk is debated within the scientific community (see section 8.1.2 which discuss the scientific robustness of the PNEC/PEC ratio).

Until the mid 2000's, data production and collection mostly focused on detection of active substances in the abiotic environment, primarily levels in water. Still very few studies documented exposure and tissue concentrations. Interest in studying toxicological and eco-toxicological profiles of medicinal products and their likely impacts on the environment (flora, fauna) and human health via the environment was only raised recently, following the discovery of the effects of Ivermectin on dung fauna (Madsen, 1990). According to a Defra representative, datasets were produced in this context, both for human and veterinary medicinal products, mostly through testing focusing on acute and hence short-term effects[82]. However, scientists and industries still have to cope with scientific, technical and economic challenges[83] associated with the assessment of environmental and health impacts of chronic exposure to medicinal products at low concentrations, in particular in the case of mixtures, as experienced by representatives from an environmental authority and a national medicine agency[84]. The understanding of the environmental and human exposure to medicinal products is still low, especially regarding birds, mammals and amphibians. In particular, there is still an undeveloped understanding of bioavailability[85] (today there is no well-established models for calculating the bioaccumulation in the food chain of medicinal products and mixtures of medicinal products residues[86]) and little consideration of the impact of the variability of environmental conditions on exposure. The difficulty to produce chronic and epidemiologic data partly explains the scarce datasets available in the literature and ultimately the difficulty to reach clear conclusions on the potential risks of a chronic exposure to medicinal products for human health, as notices a representative of environment ministry[87]. Current ERA provides information only on a few species during short-term chronic studies. Furthermore, it provides information only on the active substance concerned by the Marketing Authorisation Application. In case of a combined product, a

[81] Interviews with Dr. Bryan Brooks from Baylor University and Dr. Benoit Roig (coordinator of the KNAPPE project) carried out by BIOIS for the present study.
[82] Intervention from Defra during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012.
[83] According to an interview with Novartis, the average cost for the industry for carrying out ecotoxicological studies for one substance according to the Guideline on Environmental Risk Assessment would approximate 300.000 EUR. This information could not be retrieved in publications.
[84] Based on information provided by the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit and the Romanian national medicine agency in questionnaires elaborated by BIOIS in the context of the stakeholders' consultation for the present study.
[85] Information based on the interview with Dr. Bryan Brooks for the present study.
[86] Interview with Prof. Alistair Boxall from the University of York. Information confirmed by existing literature, e.g. in France with the work of Besse et al. (2008), which establish a preliminary classification based on the assessment of exposure, in the US with the work of US EPA (ToxServices LLC, 2008)
[87] Based on information provided by the Federal Agency for Pharmaceuticals and Health Products in Belgium (FAMPH) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.

representative of the Federal Agency for Medicinal products and Health Products from Belgium highlights that all substances are studied separately[87]. Current methods do not allow assessing the impacts of mixtures on the environment but stakeholders highlighted that a large overestimation (worst case) is often used in the calculated levels[88]. Modelling is increasingly used to cope with the lack of experimental data and assess the exposure, hazards and risks posed by medicinal products (such as Huggett Model for toxicological data (Roos, 2012)). In particular, pharmacological data can be useful to estimate the biological effects on aquatic organisms but the access to such data remains limited and the relevance of such data for environmental considerations remains to be confirmed (KNAPPE, 2008). Literature pinpoints the shortcomings of these models (e.g.in the case of Huggett Model (Schreiber, 2011)). When data is available, the lack of homogeneous and standardised methodology to produce reproducible data also impact the reliability of the data published, so that several academics recognise considering current data on medicinal products with great care[89].

These overall knowledge gaps, highlighted in NIEHS (Boxall, 2012), prevent from reaching clear conclusions on the environmental and human exposure to medicinal products and related effects.

7.5.3 Accessibility of data and transparency

Beyond the lack of data and limited knowledge highlighted in section 7.5.2, the restricted access to production, marketing and disposal data as well as existing (eco)toxicological data is also a factor influencing the knowledge's level, as shown in Chapter 2: and Chapter 3:.

Several reasons may explain the limited availability of data and the associated lack of transparency, including:

- **Confidentiality policies**: In the context of the marketing authorisation application, pharmaceutical companies are required to produce and report data related to the possible impacts of medicinal products on human health and the environment and significant datasets have been produced. However, on the request of pharmaceutical companies, assessment data are often publicly available in EPARs or national assessment reports only in the form of summaries, with limited information (see sections 8.1.2 and 8.2.4 regarding the availability of ERA data). Only medicinal products agencies or other competent authorities in charge of these dossiers have access to the information. Confidentiality reasons are partly motivated by the significant costs of testing substances and producing data and thus industries want to keep intellectual properties of in-house produced data. However, some exceptions exist: sometimes the industry agrees to release the data communicated to public authorities, and information

[88] As suggested by a representative of the Danish Pharmaceuticals Agency in the context of the present study.
[89] Based on information collected from interviews with scientific experts, carried out in the context of the present study.

considered not confidential can be published on companies or public authorities' websites[90]. See for instance the UK and ES official websites:

- www.vmd.defra.gov.uk/ProductInformationDatabase/Search.aspx
- www.aemps.gob.es/laAEMPS/portada/home.htm

- However, the level of information available in these websites is heterogeneous, and only in few cases include information related to the ERA.
- **Marketing strategies** of consultancy organisations gathering data: a number of datasets on pharmaceutical market exist that are not freely available.
- **Lack of comparable data,** in particular for veterinary medicinal products: despite antibiotics for veterinary use have been largely studied and substantial improvements have been made since 2010 through the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, experience illustrates the difficulties in standardising the presentation of data so that it can be compared or assimilated[91]. This lack of comparability is also observed regarding data on the occurrence of medicinal products in the environment. These data are available in the EU but databases are unsystematic, mostly infrequent and often represent specific local situations (which are not necessarily representative of wider regional concentrations)[92]. ESVAC is currently collecting detailed and standardised data for 2011 following a call for data sent to 27 European countries. The Agency is also planning the collection of consumption data by species[93]. Differences in inclusion criteria and conversion factors used for veterinary antimicrobial are however likely to make comparability difficult between European and national reports (EMA, 2012).
- **Fragmentation of responsibilities and low coordination of stakeholders**: production, collection and publication of data are performed by various (public or private) organisations depending on the stage of the medicinal products' life cycle. For example, medicinal products agencies are not in charge of the fate and behaviour of medicinal products in the environment. This is more likely to be the responsibility of environmental agencies. However, these organisations do not systematically monitor these substances in the environment. Furthermore, data are produced and collected at various scales, following various formats, which impedes their centralisation. For example, controls related with environmental impacts are not under the legal and technical competencies of the federal government, which grant marketing authorisations, but under the competencies of the regional administrations.

[90] Information based on the practical experience of stakeholders in the field, provided by the Institute for the State Control of veterinary biologicals and pharmaceuticals in Czech Republic and the Pharmaceuticals and Healthcare products Regulatory Agency in the UK, during interviews carried out by BIOIS for the present study.
[91] Interview with IFAH, following the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012.
[92] Based on an interview with EFPIA conducted by BIOIS for the present study.
[93] www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

7.5.4 Knowledge consolidation

The research area related to medicinal products is very fragmented. There is no clear European mechanism that aims to (i) identify key questions, and (ii) develop common efforts and coordinated research strategies in the field of medicinal products and environment. There is a need for datasets at the global/European level, with a balanced contribution from the private and public sectors. The development of European projects and international conferences appear to be a promising step towards a better coordination of efforts and the development of common strategies.

7.6 Chapter summary

7.6.1 Key messages

- Timing concerns, current costs, market demand as well as scientific and technical challenges are often evoked as obstacles to the development of efficient medicinal products with an environmentally friendly profile. Hence, pharmaceutical industries rather develop sustainable manufacturing practices on a voluntary basis.
- Beyond the need for medication, a number of factors may favour EU overconsumption (purchase and/or administration):
  - OTC medication is readily available to consumers, relatively inexpensive and can be obtained without professional advice although in some countries (e.g. UK) OTC are classified as classified as "Pharmacy" only and can only be sold under the supervision of a pharmacist;
  - prescriptions generally allow controlling the delivery of some medicinal products but over-prescription practices have been reported in a number of MS;
  - 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) and difficulties to tailor delivery (standard packaging).
  - pharmaceutical industries tend to increasingly invest in marketing activities to face decreasing innovation's momentum, controls of market authorisations and increasing generics' competition.
  - reimbursement practices may favour demand and over-prescriptions of medicinal products.

- strategies of administration (e.g. prophylactic vs. therapeutic administration; empiric vs. targeted therapies; bolus, injection, dermal) and precautionary practices during administration influence the amount of medicinal products used that is released into the environment.

- Waste management practices could be more efficient:
  - Low performance in collecting unused medicinal products in some MS can be explained by the heterogeneity in implementation of collection schemes and the lack of awareness of consumers.
  - Farms or urban areas are not necessarily designed to contain run-off.
  - Current municipal STP cannot guarantee a complete elimination of medicinal products: wastewater treatment efficiency depends on the type of technologies, the nature of substances to be treated, the concentration of medicinal products, as well as risks of sewage leakages and overflows.
  - The absence of separate collection between pharmaceutical waste and municipal solid waste does not allow deciding on a disposal option that would be the most appropriate for pharmaceutical waste (e.g. incineration or landfilling in a hazardous waste landfill). Therefore, so far, the choice of incineration or landfilling seems to depend on multiple socio-economic factors, including the presence of existing infrastructures, the capacity required and cultural preferences.
  - The agricultural valorisation of sludge and manure through land application for fertilisation purposes is increasingly observed in at least half of the MS.

- The low level of general public's and health professions' awareness of environmental impacts of medicinal products is mostly due to the difficulty to appreciate these impacts and to communicate on this issue, despite successful awareness-raising campaigns and collaborative initiatives such as Cyclamed.

7.6.2 Knowledge gaps

- Knowledge gaps were identified in previous sections. Most can be explained by the following factors:
- Although monitoring strategies and analytical methods have been remarkably improved in the last ten years, the detection of medicinal products in the environment can be limited by:
  - the heterogeneity in the selection of substances targeted,
  - monitoring gaps for certain compartments,

- `heterogeneity of sampling protocols,
- low environmental concentrations of medicinal products, and
- cost of monitoring campaigns.

- It is still debated whether current indicators of hazards and risk can or not:
  - reflect the multiple and complex possible modes of action of medicinal products (genetic, molecular, etc.).
  - identify subtle non-lethal and ecologically important effects of a chronic exposure of target as well as non-target organisms.
- Several factors may explain the limited availability of data and the associated lack of transparency: confidentiality policies, marketing strategies, lack of comparable data, as well as fragmentation of responsibilities along with a low coordination of stakeholders.
- Despite the development of European projects and international conferences, there is no clear European mechanism that aims to identify key questions, and develop common efforts and coordinated research strategies in the field of medicinal products and environment.

Chapter 8: Legislative factors of influence

The EU approach for the evaluation and control of risks to the environment from human and veterinary medicines during their life cycle (that is, from production to end-of-life) requires the review of a large number of legislative instruments which, apart from EU specific legislation on EU medicinal products, do not usually focus on or refer to medicinal products.

In this respect, the present chapter will focus on the following legislation:

- EU legislation regarding marketing authorisation of medicinal products for human and veterinary use, and in particular:
  - 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, as amended;
  - 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, as amended; and
  - Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended.
- Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), as amended;
- Good Manufacturing Practice
  - Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of food manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use; and
  - Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.
- Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control);
- 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;
- Water legislation, in particular:

- Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (Water Framework Directive);
- Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration;
- Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy;
- 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;
- Directive 2008/56/EC of the European Parliament and of the Council of 17 June 2008 establishing a framework for community action in the field of marine environmental policy (Marine Strategy Framework Directive);
- Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption;
- Commission Directive 2003/40/EC of 16 May 2003 establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters; and
- Council Directive 91/271/EEC of 21 May 1991 concerning urban wastewater treatment.

- Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste (Waste Framework Directive);
- Food legislation, in particular:
  - Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products;
  - Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in food stuffs of animal origin; and
  - Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

Each of the sections and sub-sections below will first provide an overview of the relevant pieces of legislation, before analysing them in the light of the potential environmental impacts and effects of medicinal products and discussing how these issues or, or not, taken into account.

Some of the findings in section 8.1 are based on case studies of seven active pharmaceutical ingredients. The case studies are included in Annex 3 to the present study. However, common findings drawn from these case studies are included in section 8.2, and illustrate the conclusions of section 8.1. The structure of section 8.2 will therefore different from that of other sections.

8.1 EU legislation regarding marketing authorisation of medicinal products for human and veterinary use

The marketing authorisation process for medicinal products is governed by Directives 2001/82/EC[94] for veterinary use and 2001/83/EC for human use[95], and by Regulation 2004/726 laying down Community procedures for both types of medicinal products[96], as amended.

Producers of medicinal products must obtain a marketing authorisation (MA) before they are permitted to place a product on the EU market. The MA process may follow different procedures, namely one of the procedures established by the European Union (centralised, decentralised or mutual recognition procedures) or a national procedure, when the application concerns only one MS. In most cases, the MA application must include an Environmental Risk Assessment (ERA). An ERA must be presented in the MA dossier for both human and veterinary medicines, but its weight and impact in the risk/benefit analysis differ depending on the type of medicinal products.

Special rules exist for the authorisation of medicinal products for paediatric use, orphan medicinal products, traditional herbal medicinal products, vaccines and clinical trials, which are outside the scope of this section. There are special provisions regarding e.g. advanced therapy medicinal products (in the case of medicinal products for human use) or human or veterinary medicinal products containing genetically modified organisms. However, these special provisions will not be addressed in this chapter, as it will focus on the general rules applicable to medicinal products.

Some of the findings of the present section are illustrated and highlighted by the results of case studies carried out for seven active pharmaceutical ingredients: four used in veterinary medicinal products (Ivermectin, Tylosin, Tetracycline and Doramectin) and three used in medicinal products for human use (ethinylestradiol, Fluoxetine and 5 Fluorouracil). The specifics of the case

[94] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary pharmaceuticals.
[95] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to pharmaceuticals for human use.
[96] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of pharmaceuticals for human and veterinary use and establishing a European Medicines Agency.

studies are included in Annex 3, whereas conclusions and common findings are included in section 8.2 of this chapter).

8.1.1 Marketing authorisation (MA) process

Content of MA application

EU directives regarding the MA process for medicinal products for both human and veterinary use are clear as to what the MA application must contain: these provisions are included in Article 8 and Annex I of Directive 2001/83/EC (medicinal products for human use) and in Article 12 and Annex I of Directive 2001/82/EC (veterinary medicinal products).

Existing procedures

Four procedures exist for the MA process: the three first procedures are Community procedures (centralised, decentralised and mutual recognition procedures), and the fourth is the national procedure which applies when the MA application is limited to the territory of one MS.

Pursuant to EU legislation (see section 8.1.2 below), environmental risks are included in the risk/benefit analysis for veterinary medicinal products, but not for medicinal products for human use. Consequently, a MA may be refused on environmental grounds only for veterinary medicinal products.

Centralised procedure

This procedure came into operation in 1995, following the legislation creating the European Agency for the Evaluation of Medicinal Products in 1993 (EMEA, now the European Medicines Agency –EMA– since Regulation 2004/726). This procedure is compulsory for certain medicinal products listed in the Annex to Regulation 726/2004[97], and optional for any other products containing new active substances not authorised in the Community before 20 May 2004 (when Regulation 726/2004 entered into force) or for products which constitute a significant therapeutic, scientific or technical innovation or for which a Community authorisation is in the interest of patients or animal health at Community level[98].

The MA application is submitted to the EMA and assessed by the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Medicinal Products for Veterinary Use (CVMP) depending on the use of the medicinal product for which a MA is required. The CHMP and CVMP are part of EMA (pursuant to Articles 5 and 30 of Regulation (EC) No 726/2004). They are responsible for drawing up the opinion of the EMA[99]. The CHMP or CMVP appoints one of its members as rapporteur and one as co-rapporteur[100] (EMA, 2012b) (EMA, 2009). Figure 9 below

[97] Products derived from biotechnology, orphan medicinal products, veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth or to increase yields from treated animals, and medicinal products for human use which contain an active substance authorised in the Community after 20 May 2004 and are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.
[98] See Article 3(1) and (2) of Regulation (EC) No 726/2004, supra.
[99] Articles 5 and 30 of Regulation (EC) 726/2004, supra.
[100] See Article 62 of Regulation (EC) 726/2004, supra.

gives an overview of the MA application process under the centralised procedure (reference to CHMP is also applicable to CVMP)[101].

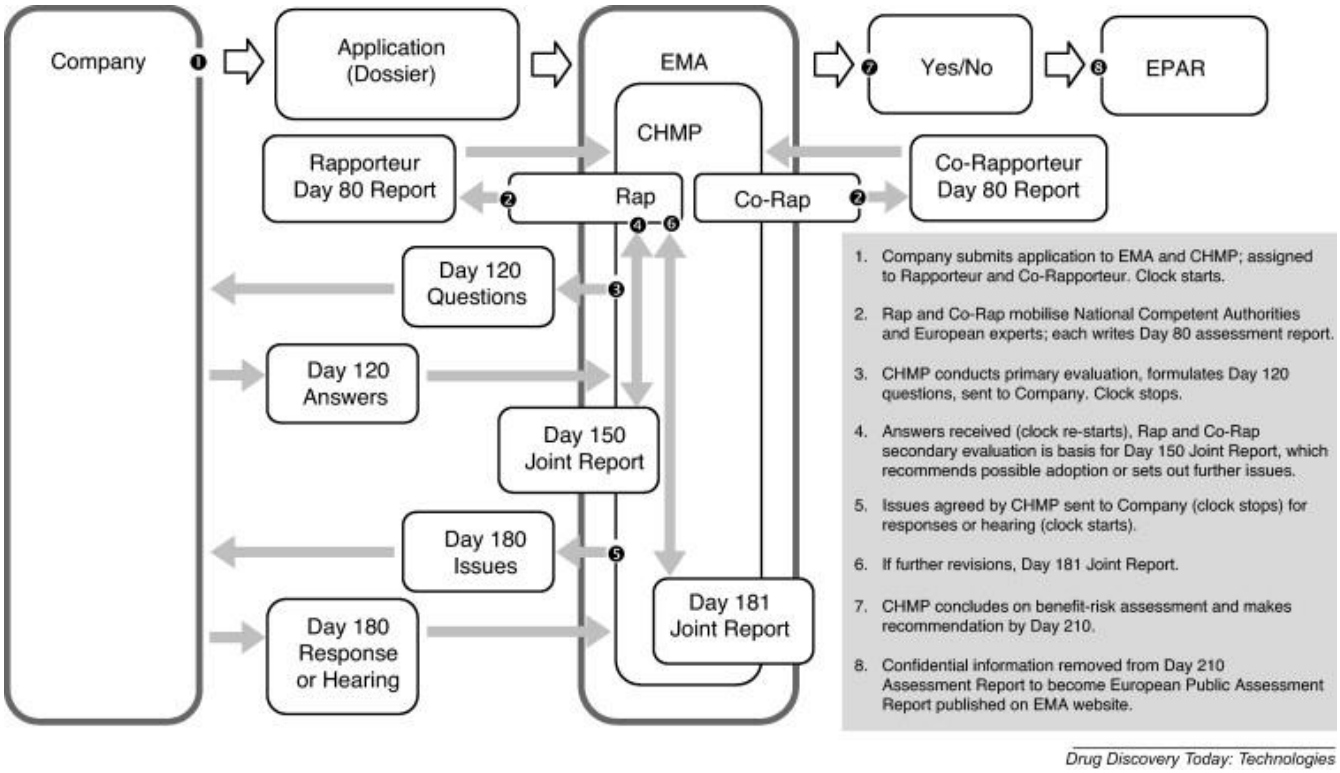

Figure 9: The centralised procedure for approving medicinal products in the European Community. Grey arrows indicate information flows (Phillips, 2011)

The composition of the CHMP and the CVMP is also important as only the CVMP has a member appointed specifically due to his expertise on environmental risk assessment. Indeed, the CVMP is composed of members nominated for each of the 27 MS, and for Iceland and Norway, and of up to 5 co-opted members who provide additional expertise in a particular scientific area. The CVMP thus includes an environmental risk assessor among these co-opted members[102], and other environmental experts in its working party on environmental risk assessment. The CHMP is composed of the same number of members, who are chosen in the same way. However, none of the CHMP co-opted members is an environmental risk assessor[103]. The rapporteur, whether nominated by the CVMP or the CHMP, must be supported by a team of national experts in the different areas of the assessment[104]. However, not all MS have experts with enough ERA

[101] See Title II Chapter 1 (for human medicinal products), and Title III Chapter 1 (for veterinary medicinal products) 'Submission and examination of applications – Authorisations' of Regulation (EC) 726/2004, supra.
[102] The current CVMP environmental risk assessor is Mr. Boris Kolar (he was co-opted in December 2007), who is the Head of Centre for risk assessment and laboratory for ecotoxicology, Institute for Public Health (Slovenian competent authority). A complete list of CVMP members is available on EMA's website:
www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000003.jsp&mid=WC0b01ac0580028eof
[103] A complete list of CHMP members is available on EMA's website:
www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000002.jsp&mid=WC0b01ac0580028c7c
[104] EMA intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Information based on the practical experience of EMA representatives in the field.

experience to perform it according to the guideline[105]; this remark also applies to the mutual recognition and decentralised procedures as developed hereafter.

The MA is ultimately granted or refused through a Commission decision[106]. The MA granted to applicants under the centralised procedure is valid throughout the EU.

▷ **Mutual recognition and decentralised procedures**

In the case of the mutual recognition and decentralised procedures, the MA application dossier is submitted at MS level: it must be identical in all MS where it is submitted. In these procedures, one of the MS acts as "reference MS" (RMS) and the other ones are "concerned MS" (CMS)[107].

The main difference between the two procedures lies in that mutual recognition applies when a medicinal product, whether for human or veterinary use, has already received a marketing authorisation in the RMS: the CMS must then recognise the marketing authorisation granted by the RMS. The decentralised procedure, which was introduced in 2004 for both human and veterinary medicinal products[108], applies to medicinal products, which have not received a marketing authorisation in a MS at the time of application (the MA application dossier is submitted simultaneously in all MS). In both cases, the RMS prepares an assessment report, which is sent to the CMS and to the applicant together with the summary of product characteristics (SPC), labelling and package leaflet[109].

A CMS may refuse to grant the marketing authorisation on various grounds, which differ depending upon whether the MA concerns medicinal products for human use or for veterinary use. In the first case, a CMS may only refuse "on the grounds of potential risk to public health", whereas in the second case the refusal may be based "on grounds of a potential serious risk to human or animal health or to the environment"[110]. The difference of grounds results in the place granted to the environmental risk assessment in the risk/benefit analysis, as will be seen below.

In case of such disagreement, all MS (reference and concerned MS) must try to reach agreement on the action to be taken. If they fail to do so, the matter is referred to the EMA; the MA may still be granted in those MS that have approved the procedure, without prejudice to the outcome of the referral procedure. The matter will be assessed by CHMP or CVMP (depending on whether the pharmaceutical is for human or veterinary use), and the Commission will take the final decision (on the granting or not of the MA)[111].

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[105] RIVM intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Information based on the practical experience of the present RIVM representative.
[106] Articles 10 and 35 of Regulation (EC) 726/2004, supra.
[107] Article 28(1) of Directive 2001/83/EC (pharmaceuticals for human use), supra, and Article 32(1) of Directive 2001/82/EC (veterinary pharmaceuticals), supra.
[108] By Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to pharmaceuticals for human use; and by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary pharmaceuticals.
[109] See Article 28(2) to (5) of Directive 2001/83/EC, supra, and Article 32(2) to (5) of Directive 2001/82/EC, supra.
[110] Article 29(1) of Directive 2001/83/EC, supra, and Article 33(1) of Directive 2001/82/EC, supra. See also Guideline on the definition of a potential serious risk to the public health in the context of Article 29(1) et (2) of Directive 2001/83/EC – March 2006, 2006/C 133/05; and Guideline on the definition of a potential serious risk to human or animal health or for the environment in the context of Article 33(1) and (2) of Directive 2001/82/EC – March 2006, 2006/C 132/08; available respectively at ec.europa.eu/health/files/eudralex/vol-1/com_2006_133/com_2006_133_en.pdf and ec.europa.eu/health/files/eudralex/vol-6/newdoc/2006_c_132_08_en.pdf
[111] Articles 29 and 32-34 of Directive 2001/83/EC, supra, and Articles 33 and 36-38 of Directive 2001/82/EC, supra. Process maps are included in the Standard Operating Procedures adopted by EMA (see pharmaceuticals for human use: www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500003004.pdf; and pharmaceuticals for veterinary use: www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC50000308 2.pdf).

The level of requirement may vary from one MS to the other, and parallel procedures for the same product can be followed in different (critical versus less critical) countries[112]. This may allow for a form of forum shopping for the granting of a MA, where the MA applicant could, under the decentralised and mutual recognition procedure, choose as RMS a country that is less critical and demanding as to the quality of the ERA performed. In addition, the decentralised and mutual recognition procedures may sometimes lead to different assessments in different MS of similar and/or different products containing the same API[113] (see sections below).

▷ **National procedure**

MAs subject to national procedures are available for medicinal products, which are to be marketed only in one MS, i.e. the MA application is limited to the territory of one MS. Depending on the MS, national procedures are not always widely used.

In France for instance, the competent authorities for assessing and delivering the MA are ANMS[114] (French Medicines Agency, for medicinal products for human use) and ANSES-ANMV (French Veterinary Medicines Agency)[115]. In Germany, about 50% of the market approvals are related to nationally authorised products. Percentages in other Member States were not available to the project team.

▶ **Supplementation of the Directives by EMA guidelines**

The provisions of Directive 2001/83/EC (medicinal products for human use) and Directive 2001/82/EC (veterinary medicinal products) are supplemented with specific guidelines adopted by the EMA. These include guidelines on ERA.

For the preparation of guidelines within the framework of Community legislation, a delegation of power is given to the European Commission (EC), which may in turn delegate the drafting of these guidelines to the EMA, in particular with regard to scientific guidelines. The procedure for the drafting and adoption of such guidelines is set forth in an EMA document (EMA, 2009b)[116]. The ERA scientific guidelines aim to provide a basis for practical harmonisation of the manner in which MS and EMA interpret and apply the requirements set forth in the relevant EU directives.

The ERA for **medicinal products for human use** is subject to the guideline adopted by the CHMP (it took 7 years for this to happen) which came into effect on 1 December 2006 (EMA, 2006).

In respect of veterinary medicinal products, the obligation to perform an ERA was first introduced in 1992 with Commission Directive 92/18/EEC[117], and in January 1997, the CVMP

[112] RIVM and UBA interventions during the Workshop on the presence of pharmaceuticals in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012.
[113] RIVM intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Information based on the practical experience of the present RIVM representative.
[114] Agence nationale de sécurité du médicament et des produits de santé, which replaced AFSSAPS (Agence française de sécurité sanitaire des produits de santé) in 2012.
[115] ANMV (Agence nationale du médicament vétérinaire) is part of ANSES, the French Agency for Food, Environmental and Occupational Health and Safety.
[116] The standard practices for adoption of guidelines include the following ten steps: (1) selection of topic and inclusion in the relevant EMA work programme(s), (2) appointment of rapporteur and (if necessary) co-rapporteur, (3) development of concept paper, (4) adoption and release for consultation of concept paper, (5) preparation of initial draft guideline, (6) release for consultation of draft guideline, (7) collection of comments, (8) preparation of final version of guideline, (9) adoption of final guideline for publication, and (10) publication. In the case of scientific guidelines, the steps related to the concept paper may be omitted.
[117] Commission Directive 92/18/EEC of 20 March 1992 modifying the Annex to Council Directive 81/852/EEC on the approximation of the laws of MS relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary pharmaceuticals, Part 3, A, Chap I, art. 5 'ecotoxicity'.

adopted a Note for guidance on ERA for veterinary medicinal products, which came into force in January 1998 (EMA, 1998). The wording, and therefore the content of this obligation, evolved with Directive 2001/82/EC. The main guidelines were drafted and approved by the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products) Steering Committee, and then submitted to the CVMP for adoption (CMP experts were involved in the work for the development of the VICH guidelines). The ERA is now carried out in accordance with the VICH guidelines approved by EMA (CVMP), namely VICH guideline 6 ("GL6") regarding Phase I (VICH, 2000) and VICH guideline 38 ("GL38") on Phase II (EMA, 2004), and the CVMP Guideline on environmental impact assessment for VMPs in support of the VICH guidelines GL6 and GL38 (VICH-TGD) (EMA, 2007). However, the CVMP has further ERA guidelines that are not VICH guidelines, some of which have not yet reached the adoption phase[118].

8.1.2 Environmental risk assessment (ERA)

The content of the MA application must include an ERA which is to be performed in accordance with guidelines adopted by the EMA (CHMP and CVMP), which include specific scientific requirements. However, an ERA is not required for all human or veterinary medicinal products (see below the section "Medicinal products for which an ERA is required") and, in addition, the weight granted to environmental risks in the MA application is not the same, whether dealing with human or veterinary medicinal products, although both directives require that an ERA be performed. The availability of ERA data and results also varies depending on the type of MA procedure followed and the MS involved.

- **Environmental risk content of the MA application**

  - **Medicinal Products for human use**

Article 8 of Directive 2001/83/EC (**medicinal products for human use**) provides that the MA application must be accompanied by, among other particulars and documents:

- Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged (art.8(3)(ca));
- Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment (art.8(3)(g)).

However, the results of tests assessing the potential environmental risks posed by the medicinal products for human use are not listed among the results of tests to be included in the MA application (art.8(3)(i)).

  - **Medicinal products for veterinary use**

[118] See the documents listed on EMA's website: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000384.jsp&mid=WC0b01ac058002dd37#Environmentalriskassessment

In comparison, Article 12 of Directive 2001/82/EC (**veterinary medicinal products**) states that the MA application dossier must notably include:

- reasons for any precautionary and safety measures to be taken when storing the veterinary medicinal product, administering it to animals and disposing of waste, together with an indication of potential risks that the veterinary medicinal product might pose to the environment, to human and animal health and to plants (art.12(3)(g);
- results of tests assessing the potential risks posed by the medicinal product for the environment. This impact shall be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it (art.12(3)(j)).

The mention, for medicinal products for both human and veterinary use, of the need to evaluate the potential environmental risks posed by the products to the environment refers to the requirement to carry out an ERA, which will be detailed below. As will be seen thereafter, the ERA results are taken into account in the risk/benefit analysis only with regard to veterinary medicinal products.

The reference in both Directives to precautionary and safety measures relates to the necessity of taking risk mitigation measures (RMM), which will be discussed thereafter.

Medicinal products for which an ERA is required

Medicinal products for human use

In respect of **medicinal products for human use**, an ERA is required in the following cases[119] (EMA, 2006):

- New MA applications submitted after 30 October 2005[120];
- Type II variations ("major variations")[121], but only if an increase in environmental exposure is expected. However, the MA holder can use the environmental data previously submitted in the original dossier;
- Extension applications according to Annex II of Commission Regulation (EC) No. 1085/2003, if there is a potential increase in the environmental exposure;
- Generics, as defined under the Directive[122].

It results from the above that medicinal products marketed before 30 October 2005 are not subject to the obligation of carrying out an ERA. Indeed, although an "*indication of any potential*

[119] See Directive 2001/83/EC as amended, supra; and Q&A on (EMA, 2006) Guideline (EMA/CHMP/SWP/44609/2010).
[120] Date of entry into force of Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to pharmaceuticals for human use.
[121] 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. See Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for pharmaceuticals for human use and veterinary pharmaceuticals falling within the scope of Council Regulation (EEC) No 2309/93.
[122] Article 10(2)(b) of Directive 2001/83/EC on pharmaceuticals for human use defines a 'generic medicinal product', for the purpose of MA application and authorisation, as "a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies".

risks presented by the medicinal product for the environment" is required since January 1995, when Directive 93/39/EEC entered into force[123], the requirement for an evaluation of potential environmental risks was introduced only by Directive 2004/27/EC (amending Directive 2001/83/EC), which came into force on 30 October 2005.

Hence, the environmental risks of numerous active pharmaceutical ingredients authorised (through their inclusion in medicinal products) before 2005 and still widely consumed have not been assessed (Paracetamol, Levothyroxin, etc.). In Germany for instance, no ERA is available for certain medicinal products for human use that contain active substances that have been measured at high concentrations in surface water[124].

In addition, as previously indicated, the ERA guideline on medicinal products for human use came into effect on 1 December 2006, which means that MA applications submitted between 30 October 2005 and 1 December 2006 do not include an ERA performed in accordance with the adopted CHMP guideline. Consultation of reports regarding authorisations granted by EMA (under the centralised procedure) during this interval tends to show that, for certain medicinal products, MA applicants used the draft guidelines. However, this may not be affirmed for all medicinal products, as the information is not available. Additionally, the market of medicinal products has reached a level of stability and the arrival of new active pharmaceutical ingredients on the market is likely to remain minor when compared to the past.

Furthermore, the CHMP ERA guideline states that in some cases the absence of an ERA could be justified (in the case e.g. of MA applications for generic medicinal products or type II variations), insofar as a rationale is provided for such absence, taking into consideration a possible significant increase of environmental exposure to the medicinal product substance. The "questions and answers" released by EMA (CHMP) on said guideline slightly differs, as it indicates that the justification of the absence of significant increase of the environmental exposure could be accepted to justify the absence of a complete ERA (and not the absence of an ERA altogether)[125]. A practical example is provided with the medicinal product Fluoxetine 20 mg hard capsules (included in the case studies), for which the UK acted as RMS: no ERA was provided and the Medicines and Healthcare products Regulatory Agency (MHRA) indicated that "*suitable justification has been provided for non-submission of an [ERA]. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an [ERA] is accepted*"[126]. Such practice is used in a large majority of MS.

In addition, no ERA has to be performed for authorisation renewals, Type IA and IB variations[127], not for substances such as vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines, and herbal products[128].

[123] Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products. Article 4.6 of Council Directive 65/65/EEC of 26 January 1965 was modified as follows: "If applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of wasteproducts, together with an indication of any potential risks presented by the medicinal product for the environment".

[124] Surface water concentrations of 10 active substances were measured in Germany in 2001, the maximum measured concentrations ranging from 0.35 µg/L to 1.81 µg/L. See UBA presentation, Pharmaceutical authorisation – Strengthening Environmental Aspects, slide 14, Paris, 21 September 2010.

[125] See CHMP Guideline, p.10, and Q&A, question no 1, supra.

[126] See www.mhra.gov.uk/home/groups/par/documents/websiteresources/con183929.pdf

[127] See Commission Regulation (EC) No 1085/2003 of June 2003, supra.

▷ Medicinal products for veterinary use

In respect of **veterinary medicinal products**, an ERA must be performed for VMPs for all types of MA applications, including for new products, generics, type II variations, extensions, etc[129]. However, it results from the applicable guidelines that in practice environmental information is not required for a certain number of products. Indeed, the decision tree (see Figure 10) implies that some medicinal products will for instance not be subject to any calculation of the predicted environmental concentration.

In light of the decision tree (Figure 10), the following veterinary medicinal products may not be subject to the obligation to provide environmental information for the ERA:

- electrolytes, peptides, proteins, vitamins, and other compounds that occur naturally in the environment (question 2 of the decision tree);
- medicinal products for pets (non-food animals, see question 3), medicinal products intended for use in a minor species that is reared and treated similarly to a major species for which an ERA already exists (question 5); and
- medicinal products used to treat a small number of animals within a flock or herd.

Application of the Phase I decision tree thus leads to many veterinary medicinal products being exempted in practice from the requirement to provide environmental information for the ERA. It means that, in practice, environmental information is required only for medicinal products to be administered to an important number of animals within a flock or herd composed of food animals[130] (CGEDD, 2010). The applicable guideline thus narrowed the scope of veterinary medicinal products having to undergo a thorough ERA.

[128] See CHMP Guideline, supra, p.3
[129] See Directive 2001/82/EC, supra, in particular Articles 12 and 13, and title on immunological veterinary products.
[130] Phase I decision tree.

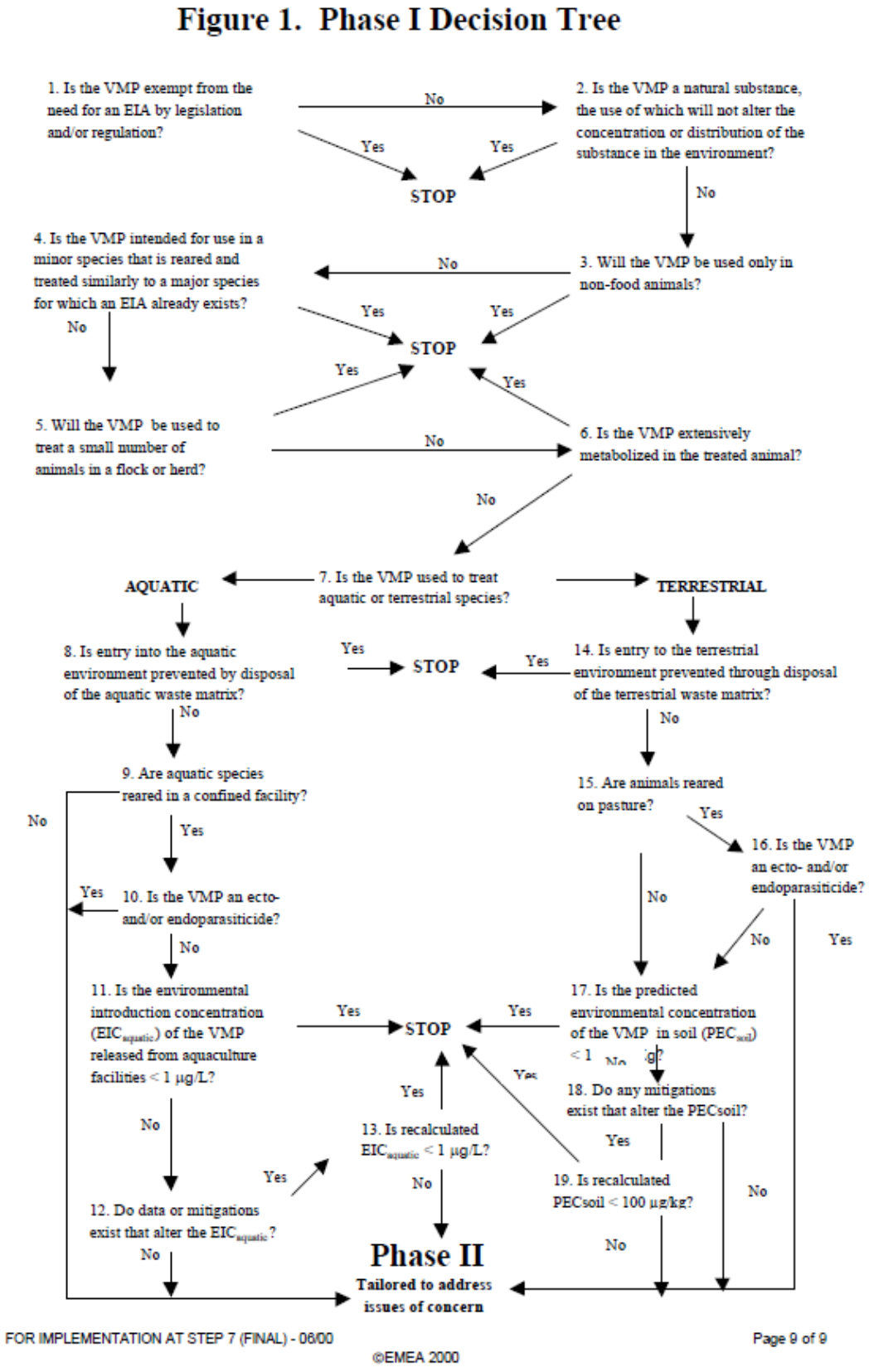

Figure 10: Phase I Decision Tree for veterinary medicinal products VICH GL6 (EMA, 2000).

▷ Limitations on re-use of ERAs for human and veterinary medicinal products

In addition, whether a pharmaceutical is for human or veterinary use, an ERA will be required for every medicinal product to be put on the market, notwithstanding the fact that an ERA may have been previously performed for another medicinal product using the same active pharmaceutical ingredient. This means that an ERA must be performed regardless of the fact that different products might have the same active substance, and that this active substance might have been previously assessed. However, the related information cannot be reused as it is deemed confidential and therefore protected. Indeed, synergies of industrial stakeholders' evaluation efforts are not possible under the current framework, as applicants are very keen on protecting all data submitted during the MA process, arguing that it would otherwise give an unfair advantage to a possible competitor who will not have had to incur the same level of costs (e.g. in the case of generics). Indeed, the applicants must own the data submitted (do their own tests) or submit data from the public domain to a reliability assessment. Apart from being inefficient and costly, it may also result in inconsistent conclusions between applications as the same active substance could thus be considered as posing environmental risks in one case and none in another. In addition, if a competent authority knows from other MA applications that an active pharmaceutical ingredient has a lack of environmental risk, the dossier must still be complete and include the ERA, with a repetition of previous studies.

Moreover, as pointed out by one competent authority, endpoints from other procedures are never accepted. Furthermore, lack of dossier completeness introduces economic issues: for instance, under the decentralised procedure a MS acting as RMS could require the submission of a full dossier from one MA applicant, whereas another MS (also acting as RMS, but in another procedure) could accept a dossier with only endpoints from another applicant. In such a case, the time and costs borne by these applicants will greatly vary.

▶ ERA guidelines: scientific requirements

▷ Description of requirements for human and veterinary medicines

The ERA, whether for medicinal products for human or veterinary use, is a tiered assessment, which includes two phases: Phase I and Phase II (including Tier A and Tier B). This means that not all products will undergo the same level of scrutiny, the thorough assessment of products (in Phase II) being performed only if they preliminarily fulfil a number of key criteria, namely related to exposure (in Phase I). The principal idea behind the concept of tiered approach is that a hazard assessment is not necessary if the environmental concentration of the tested product is not likely to trigger effects on potentially exposed species.

If exposure is considered significant under Phase I (based on the estimation of possible exposure: PEC = predicted environmental concentration[131]), then, in Phase II, the environmental risk assessment of medicinal products for both human and veterinary use involves the calculation of a risk quotient –RQ– (PEC/PNEC). This ratio is based on the estimation of possible exposure and concentrations with possible effects (PNEC = predicted no-effect concentration).

A PBT screening should always be performed for human medicinal products and, if considered, relevant also a further assessment should be performed according to REACH guidance on PBT,

[131] Or exceptionally EIC = Environmental Introduction Concentration.

regardless of whether the substances' environmental concentrations meet the trigger value under Phase I. On the contrary, for veterinary medicinal products, a PBT/vPvB assessment must only be performed during Phase II of the ERA, and therefore depends on whether the substance met trigger values under Phase I (in terms of environmental concentrations). Moreover, no specific guidance is available on how to include this PBT assessment in the risk-benefit analysis or on which risk management measures would be needed in order to grant the MA for a veterinary pharmaceutical presenting PBT properties. In practice, the multiple approaches for PBT assessment available in legislation raise the question of the consistency of such assessments, across regulatory frameworks (Box 6).

Box 6: Heterogeneity of approaches for PBT assessment and risk management

A PBT assessment is planned under several regulatory frameworks for chemicals commercialised and used in Europe. The REACH Regulation is the most frequently applied framework for PBT assessment and includes a detailed description of criteria for the identification of PBT and vPvB substances which are listed in Annex XIII. However, REACH provisions on PBT assessment do not apply to all substances on the EU market, including human and veterinary medicinal products, which have a dedicated framework for the PBT assessment, indeed very similar to the one specified in Annex XIII.

Substances may also be evaluated for PBT properties within international agreements, such as the Oslo Paris Convention (OSPAR), the IMO Ballast Water Management Convention, the UNECE POP Protocol, and the UNEP Stockholm Convention on Persistent Organic Pollutants (POPs), which all have their own set of PBT or POP criteria.The different approaches use only limited or dissimilar PBT assessments, or do not consider the issue at all. This heterogeneity might lead to relevant lack of coherence.

Similarly, the risk management follow-up of a PBT or vPvB identification, which may include a socio-economic analysis, also depends on the legal framework and the specific conditions under which a substance is used (Moermond, 2012).

Medicinal products for human use

In respect of medicinal products for human use, the relevant guideline provides that in Phase I ("estimation of exposure"), the estimation of environmental concentrations should be based only on the medicinal product substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion. Phase I must include:

- screening for persistence, bioaccumulation and toxicity (PBT) for medicinal product substances with a log Kow >4.5; and
- calculation of the Predicted Environmental Concentration (PEC) in surface water (mostly based on consumption data and market penetration factor).

According to ERA procedures, for human medicinal products, a PBT screening should always be performed and, if considered relevant, also a further assessment should be performed according to REACH guidance on PBT[132], regardless of the fact that the substance environmental concentrations meet the trigger value or not (Phase I). The results of the PBT assessment have up

[132] See Q&A on (EMA, 2006) Guideline (EMA/CHMP/SWP/44609/2010), question 4.

to now no consequences on MA for human medicinal products, since they are not considered in the risk/benefit analysis, as the rest of ERA results. Thus, even if the results of ERA highlight the environmental risk and PBT status of a substance, it is unclear which policy can be followed to manage human medicinal products with proven PBT or vPvB properties (Moermond, 2012).

PEC is estimated based on worst-case scenarios but also considering a number of simplifying assumptions, including that the sewage system is the main route of entry of medicines into the surface water and that there is no retention of the medicines in the wastewater treatment plant (e.g. through adsorption to sludge). Furthermore, metabolisation is not taken into account.

If the PEC value is below the action limit value set at 0.01 µg/L, it must be concluded that the medicinal product is unlikely to represent a risk for the environment. The ERA stops there, without the need to proceed to Phase II for the environmental fate and effects analysis. In the other case, then a Phase II analysis must be performed. A Phase II analysis must also be carried out for medicinal product substances that may act as endocrine disruptors lower than 0.01 µg/L. These must enter Phase II in any case. In Phase II, Tier A aims to assess the PEC/PNEC quotient of the substance tested. Tier B, which consists in an "extended environmental fate and effect analysis", will be in most cases required if the risk quotient (PEC/PNEC) is > 1[133]; only then will metabolites be taken into account. In this context, all relevant data should be taken into account, e.g. data on physical-chemical properties, primary and secondary pharmacodynamics, toxicology, metabolism, excretion, degradability and persistence of medicinal product substance and/or relevant metabolites.

Figure 11 below provides an illustration of the tiered approach for ERAs for medicinal products for human use.

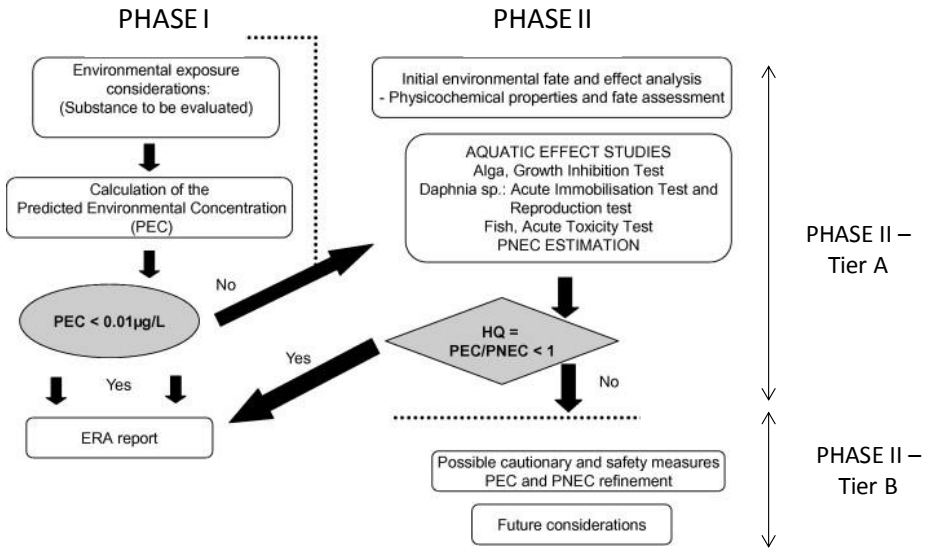

Figure 11: Scheme of the tiered approach of the EMA for environmental risk assessment for medicinal products for human use (García-Galán, 2009)

[133] See ERA guideline for pharmaceuticals for human use (EMA, 2006), supra, p.7, on outcome of Tier A fate and effect analysis, where it is precisely indicated when a Tier B extended environmental fate and effects analysis is required. When PNEC is estimated in microorganisms, Tier B is required when PEC(in surface water)/PNEC(in microorganisms) > 0.1.

Medicinal products for veterinary use

Similarly, in respect of veterinary medicinal products for which environmental information must be performed for the ERA (in particular those which assessment was not stopped following the application of the Phase I decision tree), if the medicinal product concentration in the environment is considered as being below a certain action limit concentration ($EIC_{AQUATIC}$[134]< 1 µg/L for aquatic species reared in a confined facility, and PEC_{SOIL} < 100 µg/Kg for terrestrial species, after recalculation when mitigation exists), products are not further studied in Phase II. Yet, as in the guidelines for human medicines, the action limit threshold is not applicable for some compounds that are known to be active at very low concentrations and for which a Phase II is required. These include ecto- and/or endo-parasiticides for aquatic species reared in a confined facility and for pasture animals (questions 10 and 16 of decision tree), or medicinal products aimed at treating aquatic species that are administered directly into the aquatic compartment (see question 9). Phase II is based on a risk quotient approach (PEC/PNEC) relating to non-target organisms. Phase II distinguishes between three branches: the aquaculture branch, the intensively reared animals' branch and the pasture animals' branch. For all three branches, if the risk quotient is above a certain threshold when performing Tier A of Phase II (RQ ≥ 1 for one or more tested taxonomic levels), the initial PEC must be refined; only at this refinement stage are metabolism/excretion data taken into account for PEC calculation. If, following such refinement, the risk quotient is still above the threshold, a Tier B assessment must be carried out, with further testing required.

A PBT/vPvB assessment must also be performed during Phase II of the ERA, and consequently depends on the substance having met trigger values in terms of environmental concentrations under Phase I. This approach for veterinary medicinal products could be challenged since, by definition, the PBT assessment is a hazard assessment measuring the hazardous properties of a substance, independently from its environmental concentrations and Phase II trigger values. In practice, the PBT assessment is only performed for compounds for which the predicted environmental concentration exceeds a certain threshold value, and for compounds that are not exempted (in practice) from performing an environmental risk assessment for any other reasons. Furthermore, although at the end of the evaluation, the results of the PBT assessment need then to be weighed through a risk–benefit analysis, to date there is no specific guidance on how to do so or which risk management measures would be needed in order to grant the MA for a veterinary medicinal product presenting PBT properties.

Figure 12 below provides an illustration of the tiered approach for ERAs for veterinary medicinal products.

[134] EIC is the environmental introduction concentration, i.e. the concentration in effluent.

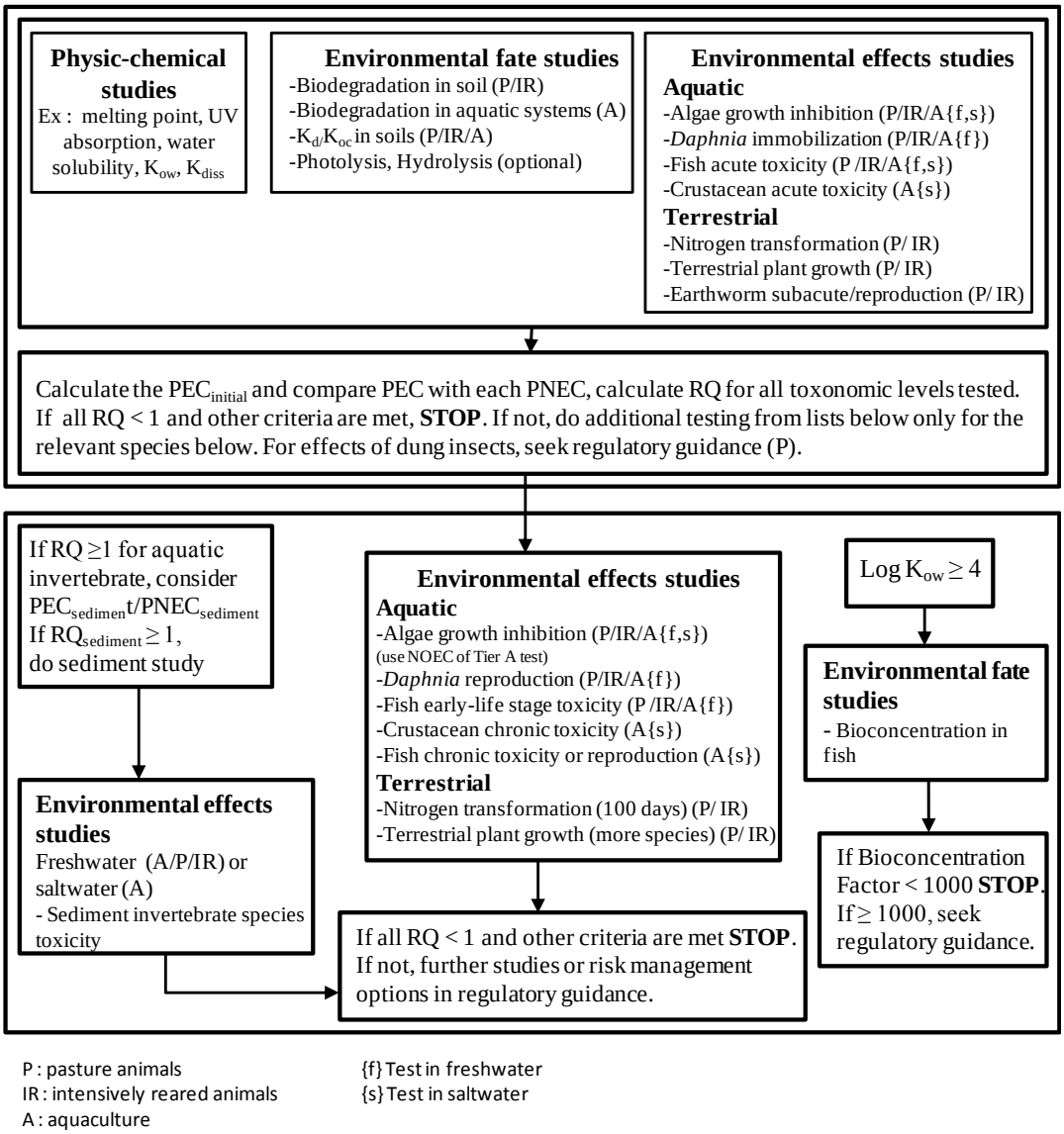

Figure 12: Environmental risk assessment of veterinary medicinal products – decision tree Phase II (adapted from CVMP guidelines (EMA, 2007))

▷ Discussion of scientific robustness regarding medicinal products for both human and veterinary use

For both types of guidelines (veterinary and human use), a number of assumptions and criteria related to exposure-based waiving assessment are subject to discussion. Their key scientific shortcomings are similar.

The main issues debated concern the relevance of the action limit values set and the indicators used to assess effects. Issues debated are listed below.

The action limit values defined in the ERA guidelines determine the number of medicines that will be exempted from a thorough environmental assessment. In this respect, their relevance may have great impacts on the good status of the environment and/or on human health. In order

to ensure the validity and credibility of the action limit values, Prof. Backhaus, nominated expert for this study, suggests that their determination meets the following criteria[135]:

- the data that are used for establishing the trigger values must be an unbiased representation of the total pool of medicinal products that can be expected to occur in the environment;
- the trigger value must represent an adequate lower percentile of the distribution of ecotoxicity data;
- the data have to be of sufficient quantity and quality and should be publically available for scrutiny (transparency);
- the underlying ecotoxicological data are analysed using state-of-the-art statistical and biometrical methods; and
- exposure-based waiving is only applicable if there are no reasons for specific concern.

Exposure-based waiving certainly has a huge potential for prioritising medicinal products for retrospective assessments and to focus experimental resources on the environmentally more problematic medicinal products. The action limit of 0.01 µg/L set in the guideline for the environmental assessment of medicinal products may be revised in the future to better reflect environmental exposure but it is based today on a conservative approach. Such trigger values conceptually resemble the use of the "general precautionary value" (GOW, *gesundheitlicher Orientierungswert*) that the German Federal Environmental Agency recommends for an initial safety assessment of pharmaceutical residues in drinking water (Umweltbundesamt, 2003), which is set at a trigger value of 0.1 µg/L. It is also analogous to the TTC/ecoTTC concept (de Wolf, 2005) (EU Scientific Committees, 2008) which is used e.g. for the health assessment of genotoxic impurities in medicinal products (EMA, 2006b). However, several examples are documented in the literature where medicinal products directly cause effects at concentrations near or even below their respective trigger values (e.g. the anti-mycotic agent Clotrimazole[136] which affects algal communities at picomolar concentrations - Porsbring, 2009; OSPAR 2013)). In the same way, the veterinary medicinal product for companion animals, medetomidine (authorised for sedation and analgesia in dogs and cats only) starts to inhibit barnacle settling around 10 ng/L (Dahlström , 2000). The examples given in this paragraph show that the action limit of 0.01 µg/L (i.e. 10 ng/L) is in the majority of cases conservative enough and consistent with the lowest concentration where environmental effects can be observed, even if a few exceptions exist. By contrast, a higher limit of 0.1 µg/ would be too high. However, it is unclear whether the current action limits are sufficiently protective when possible effects of mixtures are considered.

[135] Interview with Prof. Thomas Backhaus, Professor at the University of Gothenburg and nominated expert for the present study.

[136] The OSPAR report indicates an inhibition of algal 14á-demethylase already at environmental concentrations. The OSPAR report states that this point would merit to be studied in more detail with realization of single tests species for example. Before that, this result cannot be used to calculate the PNEC but it should be taken into account for "T" criteria evaluation.

In this respect, the action limits of 0.01 µg/L and 100 µg/kg were challenged and lower values of 0.004 µg/L and 1 µg/kg were recommended, respectively (Montforts, 2005).

In addition to these aspects, data requirements regarding ecotoxicological effects are very limited[137], namely because thorough testing is not required in Phase I of the ERA and it is indicated that exposure and effects can be estimated through modelling.

Although PEC/PNEC quotients are considered a pragmatic approach to assess risk and are well detailed by the European Commission, respective uncertainties related to the estimations of PNEC and PEC limit their relevance (UNEP/IPCS). In the field, an interview with a representative of a national environmental agency[138] pointed that the PEC/PNEC ratio has been scientifically developed and evaluated through extensive studies, and further used in numerous experiments. The results and uncertainties of this method are therefore well known and could be assessed quantitatively and qualitatively. Yet, some stakeholders question the full relevance of this indicator because, despite the requirement for chronic data in the EMA Guidelines, current PNEC values may be based on acute studies when chronic data is not available. In addition, PNEC values are often based on mortality[139], whatever the use of acute or chronic data. Furthermore, PEC values rely on estimations made in specific environmental conditions. They have been criticised for not taking into account the variability of conditions that can significantly influence environmental concentrations of medicinal products (presence/absence and type of manufacturing sites, level of pharmaceutical use, population demographics, cultural practices, environmental and climatic characteristics, dilution potential of receiving environments and infrastructure related to wastewater and drinking water treatment, etc[140]. Conclusions from the KNAPPE project highlight that the use of simple models, as the EMA model, to calculate PECs for surface water is in general in good agreement with field measurements (KNAPPE, 2008). However, PEC for other compartments than water column would not be well assessed.

The ERA framework has been considered as not being optimal with regards to the specificities of medicines compared to other chemicals (e.g. biocides), namely because it especially relies on endpoints such as "death" that do not adequately reflect sub-lethal and ecologically important effects related to chronic exposure (see section 7.5.2)[141].

ERA does not consider metabolites or environmental transformation products in the preliminary exposure assessment (for both human and veterinary medicines), which may represent significant hazard in certain cases (See Chapter 1:).

ERA mainly focuses on the aquatic compartments and only considers possible exposure from sludge and sediments in Phase II where considered relevant, although sorption during

[137] RIVM intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Information based on the practical experience of the present RIVM representative.
[138] Interview with Annette Küster, from UBA in Germany. This interview provided information on how the potential risks posed by medicinal products are assessed in practice, based on stakeholders' experience in the field, which is not necessarily publicly available.
[139] Interviews with Dr. Benoit Roig, researcher and KNAPPE scientific coordinator, and with Annette Küster, from UBA in Germany. These interviews provided information on how the potential risks posed by medicinal products are assessed in practice, based on stakeholders' experience in the field, which was not necessarily publicly available.
[140] Interview with Dr. Bryan W. Brooks, author of 85+ refereed articles and book chapters. In 2012, he published (with DB Huggett) Human Pharmaceuticals in the Environment: Current and Future Perspectives (Springer: ISBN 978-1-4614-3419-1).
[141] EEA intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Confirmed by findings from 2008 KNAPPE project.

wastewater treatment has been demonstrated and sludge reuse identified as a key contamination pathway (see section 3.3).

▷ **Heterogeneity in the interpretations of ERA guidelines and implementation**

Compliance with ERA guidelines is not uniform in the various MS, as they may interpret the guidelines differently (such difference in scientific interpretation of guidelines is however a common issue with evaluation in general and not specific to ERAs). This may therefore result in a lack of consistency concerning ERAs performed within the EU for medicinal products with the same active substance[142]. Performing an ERA may indeed raise some difficulty as MS may have different interpretations of the ERA guidelines and, as such, have different requirements and implement the ERA differently[143].

EMA recognised that the ERA guidelines could be subject to multiple interpretations as regards veterinary medicinal products, although it highlighted that any disagreement between MS (in the case of decentralised and mutual recognition procedures) on the results/procedures for the ERA, in particular concerning veterinary medicinal products, may be referred to the CVMP.

It has also to be noted that depending on MS, very few or no experts with environmental background may be in charge of the assessment of ERA dossiers.

As showed in the previous sections, consumption of medicinal products is diverse in different Member States, as well are environmental conditions. In particular the size of river basins as recipients of discharged APIs or metabolites are different, and they may be easily located in different Member States. This means that 'EU-averaged approach' in risk assessment may appear not sufficient.

▶ **Impacts of the ERA results in the MA process**

▷ **Medicinal products for human use**

In the case of **medicinal products for human use**, the ERA is not part of the benefit-risk analysis. The wording of Directive 2001/83/EC is unequivocal as definitions 28 and 28a set forth in Article 1 read:

> 28. *Risks related to use of the medicinal product:*
>
> - Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;
> - Any risk of undesirable effects on the environment.
>
> 28a. *Risk-benefit balance*: An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, **first indent.**

These definitions make it clear that environmental risks are not included in the risk/benefit analysis and, therefore, the ERA results have no impact on the decision to provide an

[142] RIVM and EFPIA interventions during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. These interventions provided information on how the potential risks posed by medicinal products are assessed in practice, which was not necessarily publicly available.
[143] EFPIA intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. This intervention provided information on how the potential risks posed by medicinal products are assessed in practice, which was not necessarily publicly available.

authorisation. This is also reflected in the ERA guideline, which states that the environmental impact of such medicinal products "*should not constitute a criterion for refusal of a marketing authorisation*" (EMA, 2006), notwithstanding the type of procedure followed for the marketing authorisation (centralised, mutual recognition, decentralised or national procedures). Under the mutual recognition and decentralised procedures, this further entails that a CMS could not refuse to grant a MA to the applicant on the ground of a potential risk to the environment.

When the possibility of environmental risks cannot be excluded, risk mitigation measures will be established, as will be seen hereafter.

▷ **Veterinary medicinal products**

In contrast, the results of the ERA for **veterinary medicinal products** must be considered in the benefit-risk analysis on which the decision of authorisation is based. The relevant definitions of Article 1 of Directive 2001/82/EC provide indeed:

19. *Risks relating to use of the product:*
    - Any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;
    - Any risk of undesirable effects on the environment.
20. *Risk/benefit balance:* An evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined above.

It results from the above that, for all procedures (centralised, mutual recognition, decentralised or national) a MA for a veterinary medicinal product could be denied on environmental grounds, if the risks posed are too high (the risk/benefit balance as defined is not limited to the «first indent» as is the case with medicinal products for human use). For instance, under the mutual recognition and decentralised procedures a CMS could refuse to grant a MA to the applicant on the ground of a potential risk to the environment, notwithstanding the fact that the RMS granted such authorisation to the veterinary medicinal product. An example of a refusal to grant a MA because the ERA was incomplete (and, consequently, the MA applicant could not show that the veterinary medicinal product did not pose risks to the environment) includes the case of Pharmasin (Tylosin). Further details are provided in Section 8.2 and in Annex 3.

Another example of a referral to re-examine substances contained in veterinary medicinal products on environmental grounds include Enrofloxacine (ERA in 2009)[144].

▷ **Considerations on lack of or incomplete ERAs, applicable to medicinal products for both human or veterinary use**

The inclusion of ERA results in the risk/benefit analysis or the lack thereof also has consequences on the weight given to the ERA in the MA authorisation. In the case of **veterinary medicinal products**, a lack of ERA or an incomplete one would normally lead to a refusal of the MA. Nevertheless, there are sometimes data gaps in the material, and CVMP must then take a

[144] Suggested by FAMHP during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Confirmed by the Overall summary of the scientific evaluation of HIPRALONA ENRO-S and its generics intended for use in rabbits (see Annex I). Available at: www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Hipralona_enros_35/WC500138420.pdf

decision based on the presented material[145]. In addition, although timelines for assessment of medicinal products are well defined in law and it assumes that the dossier submitted is complete, it has been brought to the consultant's attention that, in practice, certain MS request additional information when the veterinary ERA is insufficient or incomplete[146], but time constraints may impede it.

In the case of **medicinal products for human use**, a lack of, or incomplete ERA in the MA application does not prevent the granting of the authorisation: EMA then requires a "post-authorisation commitment" to perform or complete the ERA. Such examples include the MA applications for Multaq (*dronedarone*) (incomplete Phase I: additional studies needed as follow-up measures)[147], Resolor (*prucalopride*) (Phase I provided, but full Phase II assessment required)[148] and Samsca (*tolvaptan*) (Phase I and Phase II-Tier A provided, but a Phase II-Tier B is required)[149]. However, companies are not obliged to submit this data as the ERA is not included in the risk/benefit balance. This practice has also been reported in MS acting as RMS. A recent example includes the public assessment report published by MHRA (2013) for Flurbiprofen 8.75 mg Lozenges (*Flurbiprofen*)[150]. According to UBA, in Germany 92% of ERAs are provided for human medicinal products, leading to 8% of missing ERAs; incomplete ERAs in Phase II represent 57%[151].

In addition, the inclusion of ERA results in the risk/benefit analysis also means that in the case of **veterinary medicinal products**, R&D laboratories must consider environmental impacts of medicines during the conception phase, as they will be weighed in the risk/benefit analysis. However, this does not apply to **medicinal products for human use**.

[145] Based on the results of EMA-CVMP questionnaire, from the stakeholders' consultation organised by BIOIS for the present study.
[146] Based on information provided by the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study. This questionnaire provided information on how the potential risks posed by medicinal products are assessed in practice, based on stakeholders' experience in the field, which is not necessarily publicly available.
[147] Multaq was authorised on 26 November 2009. The European Public Assessment Report (EPAR) , published on 16 December 2012, states the following with regards to ecotoxicity/ERA: "With respect to the environmental risk assessment, the following conclusions have been drawn: DRO is neither PBT nor vPvB, risk to the microorganisms in a sewage treatment plants, risk to the aquatic compartment, the groundwater compartment and the terrestrial is considered to be negligible. In order to complete the environmental risk assessment, it has been agreed that further studies, i.e. OECD 307 and OECD 308 will be performed as well as recalculation of the kinetic BCF OECD 305 fish BCF study. It has been agreed that these data will be provided as a follow-up measures (FUM 1-3)"; available at www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001043/WC500044538.pdf
[148] Resolor was authorised on 15 October 2009 and the EPAR published on 17 November 2009, www.ema.europa.eu/docs/en_GB/document_library/EPAR__Public_assessment_report/human/001012/WC500053997.pdf
[149] Samsca was authorised on 3 August 2009, and the EPAR published on 18 August 2009; available at www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000980/WC500048715.pdf
[150] Available at www.mhra.gov.uk/home/groups/par/documents/websiteresources/con231527.pdf
[151] UBA presentation, September 2010, supra, slide 11.

Availability of ERA data and results

EU legislation sets out a general principle of transparency for public access to European Parliament, Council and Commission documents, which include documents drawn up but also received by them[152]. In the field of environment, the principle of transparency and the obligations it entails are set forth in Directive 2003/4/EC[153].

Article 3(1) of Directive 2003/4/EC provides: "*Member States shall ensure that public authorities are required, in accordance with the provisions of this Directive, to make available environmental information held by or for them to any applicant at his request and without his having to state an interest*". Certain exceptions may apply to this obligation to provide access to environmental documents; such access may therefore be refused, in particular if disclosure of the information would adversely affect the confidentiality of commercial or industrial information[154]. However, these exceptions must be interpreted in a restrictive way. EMA nevertheless adopted a definition of "commercial confidential information", with regards to access to documents related to medicinal products for human or veterinary use, which may be viewed as excessively broad, as it defines it as "*any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information*" (EMA, 2006c).

Pursuant to Articles 13(3) and 38(3) of Regulation (EC) 726/2004, the EMA publishes a full scientific assessment report called a European Public Assessment Report (EPAR) for every medicine granted a central marketing authorisation by the European Commission. The EPAR must notably include the reasons for EMA's opinion in favour of granting the MA, after deletion of any information of a commercially confidential nature, as well as a summary understandable to the public. In addition, Directive 2001/83/EC (medicinal products for human use) and Directive 2001/82/EC (veterinary medicinal products) both provide that the competent authorities must make publicly available the marketing authorisation and the summary of the product characteristics[155], and mention the obligation for competent authorities to draw up an assessment report, in the same terms as those of Regulation (EC) 726/2004[156]. However, environmental data (including ecotoxicological data) and ERA results are not mentioned as having to be included in the assessment report and/or made publicly available.

In practice, some EPARs (but not all) contain a chapter called Eco-toxicology/Environmental Risk Assessment but, until recently, this was generally only a brief summary mainly focusing on the first step of the ERA, i.e. Phase I (PEC calculation)[157] (Bouvier, 2010). For instance, for the **human medicinal product** Baraclude (*entecavir*) authorised in June 2006, the EPAR (published in May 2007) only states that "*an assessment of the risk was performed and no significant risk to the*

[152] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents.
[153] 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. See also UN Economic Commission for Europe (UNECE), Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters, signed on 25 June 1998 (notably by the European Union) and which came into force on 30 October 2001.
[154] Article 4(2)(d) of Directive 2003/4/EC, supra.
[155] Article 21(3) of Directive 2001/83/EC, supra, and Article 25(3) of Directive 2001/82/EC, supra.
[156] Article 21(4) of Directive 2001/83/EC, supra, and Article 25(4) of Directive 2001/82/EC, supra.
[157] Response of French authorities to a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study

environment related to the use of entecavir is anticipated"[158]. However, even when a Phase II assessment had been carried out, only a short conclusion was available, but still no environmental data. As an example, for Avamys (*fluticasone furoate*), the EPAR (2008) provides only that "*the regulatory and scientific strategy of ERA chosen by the applicant is reasonable and the scope of studies (Phase I and Phase II, Tier 1) acceptable*"[159]. In addition, the EPAR published in October 2009 for Onglyza (*saxagliptin*) mentions only: "*A phase II environmental risk assessment was conducted for saxagliptin as the trigger value was exceeded. Saxagliptin is neither persistent, bioaccumulative or toxic (PBT) nor very persistent, very bioaccumulative (vPvB). Risk to the surface water, groundwater, soil, sediment and sewage treatment plant is acceptable*"[160]. Recent EPARs are however more exhaustive, providing a "summary of main study results", but environmental data is still generally insufficient, as EPARs (2012) for human medicinal products Seebri Breezhaler (*glycopyrronium bromide*)[161] or Xalkori (*crizotinib*)[162] illustrate. There are sometimes examples of EPARs that include environmental data (endpoints), such as for Jentadueto (*linagliptin/metformin hydrochloride*)[163]. A national competent authority nevertheless pointed out that in order to find such information, it would be first necessary to know that the information is actually in the EPAR, and then look through tens of medicinal products before finding a medicinal product concerning which an EPAR was published with environmental data.

As regards **veterinary medicinal products**, EPARs sometimes limit reference to the ERA to one sentence, notably in old EPARs. For instance, the EPAR (2002, published in 2005) for Dexdomitor (*dexmedetomidine hydrochloride*), which states that "*an acceptable environmental risk assessment for phase I has been provided*"[164]. More recent EPARs are more exhaustive. However, the various EPARs consulted do not provide much environmental information regarding the medicinal products being authorised, as the application of Phase I decision free may entail that no further assessment is required[165].

At MS level, the availability of environmental information included in the ERA varies from one State to another. For instance, in Sweden, environmental data for medicinal products in Sweden is publically available[166], but this data is not calculated along the ERA guidelines adopted by EMA. However, environmental information is not always contained in the assessment made public by

[158] The EPAR for Baraclude (entecavir) is available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000623/WC500051985.pdf
[159] The EPAR for Avamys (fluticasone furoate) is available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000770/WC500028817.pdf
[160] The EPAR for Onglyza (saxagliptin) is available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001039/WC500044319.pdf
[161] The EPAR (2012) for Seebri Breezhaler (glycopyrronium bromide) is available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002430/WC500133771.pdf
[162] The EPAR (2012) for Xalkori (crizotinib) is available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002489/WC500134761.pdf
[163] The EPAR (2011) for Jentadueto (linagliptin/metformin hydrochloride) is available at: www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002279/WC500130972.pdf
[164] The EPAR (2002) for Dexdomitor (dexmedetomidine hydrochloride) is available at : www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/veterinary/000070/WC500062496.pdf
[165] See for instance EPAR (2011) for TruScient (dibotermin-alfa), available at www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/veterinary/002000/WC500119823.pdf
See also EPAR (2012) for Activyl Tick Plus (Indoxacarb-Permethrin), available at www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/veterinary/002234/WC500120992.pdf. In this case, the ERA stopped at question 3 of Phase I decision tree because the product was not intended to be used in any food producing species. The impact on the environment was nonetheless still considered "considering the nature of the product".
[166] ERA data are available on www.fass.se. An example may be found at the following web page: www.fass.se/LIF/produktfakta/artikel_produkt.jsp?NplID=19811016000049&DocTypeID=78#IDE4POC1U973RVERT1

national medicine regulators (Keessen, 2007). This has been attributed to commercial sensitivity of data contained in the ERA[167] (Keessen, 2012), which is questionable as, as seen above with recent EPARs for human medicinal products, endpoints are sometimes published.

A number of competent authorities publish a public assessment report, within which information on the ERA can be found:

- The Veterinary Medicines Directorate (VMD) in the UK publishes, in its Product information database[168], EPAR or PAA for some substances which may include information on ERA results and risk mitigation measures, and so does the UK Medicines and Healthcare products Regulatory Agency (MHRA)[169];
- The Spanish Agency of Medicines and Medical Devices (AEMPS) provides links between its Online information centre on medicines[170] and corresponding EPARs on EMA website; it does not however seem to provide links to public assessment reports, although, in the case of veterinary medicinal products, the results provided through the research tool include such a section[171];
- Germany does not make publicly available environmental data about medicinal products for human use[172], but provides information for veterinary medicinal products[173];
- Other countries do not provide any information to the public on ERA results; it is notably the case of Belgium[174], Bulgaria[175], the Czech Republic[176] or Romania, although in this latter country, publication of such information is planned for the future[177]; and
- In France, very limited environmental information is provided by ANSM for medicinal products for human use authorised by ANSM[178] or by ANSES-ANMV for veterinary medicinal products. In the French public assessment reports consulted, this information can be a mere sentence concluding to the absence of

[167] Response of French authorities to a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[168] www.vmd.defra.gov.uk/ProductInformationDatabase/
[169] See notably www.mhra.gov.uk/Publications/PublicAssessmentReports/index.htm
[170] www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm
[171] The consultant carried out searches on AEMP's website (www.aemps.gob.es), for both human and veterinary medicinal products, and was unable to find public assessment reports. See for instance searches using the active substance ivermectina (for veterinary medicinal products) and etinilestradiol for medicinal products for human use.
[172] Based on information collected in the context of a stakeholders' consultation carried out by BIOIS for the present study. Confirmed by (EMA, 2010b)
[173] Based on information provided by the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study. For example, see the public assessment report provided for the veterinary medicinal product Cobactan (2012), available at www.anmv.anses.fr/wp-content/uploads/2012/01/COBACTAN.pdf
[174] Based on information provided by the Federal Agency for Medicines and Health Products (FAMHP) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[175] Based on information provided by the Bulgarian Drug Agency in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[176] Based on information provided by the Czech Veterinary Agency (USKVBL) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[177] Based on information provided by the Romanian National Medicine Agency (ANM) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[178] See e.g. the French public assessment report (2008) for IASOdopa, available at:ansm.sante.fr/var/ansm_site/storage/original/application/2e666bebe6bf4d7a1a542aeff11b8a64.pdf

environmental risk[179]. Consequently, this environmental information amounts to no information.

Even when published, the ERA endpoints may be hard to find[180].

Certain pharmaceutical companies may choose to make some ERA data available on their website on a voluntary basis, but it is not common practice.

8.1.3 Risk Mitigation Measures (RMM) and pharmacovigilance

When, following completion of the ERA (at the end of Phase II Tier B), the environmental risks cannot be excluded, risk mitigation measures (RMM) may be imposed on the applicant, i.e. the future holder of the authorisation. Both Directive 2001/83/EC (medicinal products for human use) and Directive 2001/82/EC (veterinary medicinal products) and their related guidelines provide for precautionary and safety measures to be taken.

- **Medicinal products for human use**

Article 8(3)(g) of Directive 2001/83/EC (medicinal products for human use) states that the MA application must provide the reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment. The relevant EMA (CHMP) guideline on ERA further specifies that such measures may consist of:

- An indication of potential risks presented by the medicinal product for the environment, in the documents communicated to the public (such as the package leaflet); and
- Product labelling, Summary of Product Characteristics (SPC), Package Leaflet (PL) for patient use, product storage and disposal. Labelling should generally aim at minimising the quantity discharged into the environment by appropriate mitigation measures.

- **Veterinary medicinal products**

In the same manner, Article 12(3)(g) of Directive 2001/82/EC provides that the MA application must give the reasons for any precautionary and safety measures to be taken when storing the **veterinary medicinal product**, administering it to animals and disposing of waste, together with an indication of potential risks that the veterinary medicinal product might pose to the

[179] See e.g. the French public assessment reports for the veterinary medicinal products Detosedan (2012), Spiramycine (2012), Antalzen (2012, national procedure), where the section on ecotoxicity only reads: "the applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed". See also the public assessment report for Cydectin Triclamox (2012) where a Phase II was performed but no relevant data is included in the report. All reports are available on the ANSES-ANMV's webpage www.anmv.anses.fr/?page_id=3292

[180] RIVM intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on September 19, 2012. Information based on the practical experience of the present RIVM representative.

environment, to human and animal health and to plants. The Directive further provides that the ERA must identify any precautionary measures, which may be necessary to reduce the risks to the environment[181]. It also states that a veterinary prescription must be required for dispensing to the public those products in respect of which special precautions must be taken by the veterinarian in order to avoid any unnecessary risk to the environment[182]. Finally, VICH GL38 also states that if an environmental risk remains after Phase II, Tier B, *"the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority"*. In this context, applicants and/or regulators may recommend inclusion of risk mitigation measures in the SPC, as well as in the product literature, with the aim of reducing environmental exposure and thereby reducing the risk to an acceptable level.

In March 2012, the CVMP adopted a "reflection paper" on RMM related to the ERA of VMPs (EMA, 2012c) that reviewed the adequacy/appropriateness of RMM included in current MA of veterinary medicinal products. This document is based on guidance document VICH-TGD, which defined several criteria aimed at ensuring greater animal owner/prescriber compliance[183] (Keessen, 2012) (EMA, 2007). The reflection paper provides examples of RMM currently in use and assesses how they match with the criteria specified in VICH-TGD, leading the CVMP to distinguish between RMM fulfilling the guideline criteria and those not fulfilling it.

Concerning RMM considered to fulfil the guideline criteria, it must be noted that fulfilling certain criteria may depend on various circumstances. Examples include the following (EMA, 2012c):

- Animals must remain stabled for <x> days after treatment, until the concentration of <active substance> in excreta is low enough to avoid adverse effects on dung fauna and their predators. In this regard, the reflection paper indicates that the number of days has to be in agreement with acceptable agricultural practice and can only be applied to animals that can be stabled, adding that stabling of animals for prolonged periods may not be feasible (e.g. in the middle of the grazing season);
- A discharge consent by local water authorities is required before use of <product>, because the concentration of the active substance in surface water must not exceed <x> to avoid adverse effects on the aquatic environment. This RMM, related to a risk identified for a veterinary medicinal product used in fish farms, would be effective only in countries where local authorities monitor the use of products and their discharge from aquaculture facilities, i.e. in MS with discharge consent (or similar) systems.

[181] Annex I, Title I, Part 3(A)(6.1) (VMP other than immunological VMPs) and Title II, Part 3(D) (immunological VMPs) to Directive 2001/82/EC, supra.
[182] Article 67(b) of Directive 2001/82/EC, supra.
[183] The VICH-TGD (EMA, 2007), supra, provides: "To be effective such a risk mitigation measures should meet the following criteria: 1- Mitigate exposure of the veterinary medicinal product to the environment; 2- Be in line with agricultural practice (when used in food producing species); 3- Be in agreement with the legislation of the EU and its MS; 4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included. If as risk mitigation measure does not fulfil the criteria mentioned above then the outcome of the risk assessment is that a serious risk for the environment exists. In accordance with Directive 2001/82/EC (as amended) this risk has to be weighed against the favourable aspects of a marketing authorisation". Also, Response of French authorities to a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.

With respect to RMM considered as not fulfilling the VICH-TGD guideline criteria, the reflection paper distinguishes between measures under the control of the veterinarian or animal owner and those not under their control. In the first case, an example of such RMM would be to not treat animals on the same pasture in successive seasons to avoid adverse effects on dung fauna and their predators; but the farmer might not have the possibility to rotate pasture and/or the measure could be against the health/welfare requirements of the animals treated (e.g. where the treatment in question is the treatment of choice)[184] (EMA, 2012c). Examples of RMM not under the control of the veterinarian or animal owner mainly relate to the spreading of manure[185] (EMA, 2012c), the difficulty being linked notably to the fact that the manure spreader may be a third party and therefore not informed of the RMM. For instance, if the RMM is that a minimum distance to surface water of <x> meters be applied when spreading manure, the CVMP further indicates that this measure may only be suitable for national authorisations in countries without manure trading, but could not be included in agricultural practice in countries where manure trading is common and where no prior consent is required for manure spreading.

It results from the above that, in respect of veterinary medicinal products, it is very complex to control the application of RMM and ensure a thorough follow-up. In addition, there is no clear responsibility regarding their implementation, which results in the existence of procedural gaps.

- **Considerations applicable to both human and veterinary medicinal products**

When an ERA highlights environmental risks of a medicinal product, whether for **human** or **veterinary** use, which is authorised for marketing, EU legislation does not provide any obligation to carry out monitoring of environmental risks once the authorisation is delivered, or pursuant to a decision to withdraw or modify RMM[186].

However, EU legislation requires that a pharmacovigilance system be established and administered for medicinal products for human and veterinary use, which entails a certain number of obligations of the MA holder. Nonetheless, available information on potential environmental problems must be taken into account only for the veterinary parmacovigilance system[187]. However, according to a national competent authority, there is no control mechanism in place and therefore few insights regarding the efficiency of its implementation. For human medicinal products, the emerging environmental problem that the pollution of waters and soils with residues of medicinal products represents is acknowledged in recitals to EU pieces of legislation, but there is no obligation to collect and report information on environmental risks of human medicinal products[188]. However, Regulation (EC) No 726/2004 (as amended) provides that where urgent action is essential to protect human health or the environment, a MS may, on its own initiative or at the Commission's request, suspend the use in its territory of a medicinal product, whether it be for human or veterinary use[189].

[184] CVMP reflection paper (EMA, 2012c) supra, pp.6-7.
[185] CVMP Reflection paper (EMA, 2012c), supra, pp.8-9.
[186] Based on information provided by the RIVM in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[187] Article 73 of Directive 2001/82/EC, supra.
[188] See Recital 6 of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending Directive 2001/83/EC; and Recital 3 of Regulation (EU) No 1235/2010 of the European Parlliament and of the Council of 15 December 2010 amending Regulation (EC) No 726/20047.
[189] Regulation (EC) No. 726/2004, supra, Articles 20(4) (human medicinal products) and 45(4) (veterinary medicinal products).

As previously mentioned, the MA imposes on the authorisation holder to indicate precautions for safety and health protection including measures to mitigate the risk for the environment on the medicinal product's packaging or on the leaflet. However, this requirement is legally binding only for the authorisation holder; it has only an informative value for prescribers and consumers. This point was reaffirmed notably by the CVMP, which noted in its above-mentioned reflection paper that "*there is no legal basis for the enforcement of any risk mitigation measures recommended on the SPC*"[190] (EMA, 2012c). Compliance with RMM has therefore only a voluntary character, unless of course rules from other – European or national – regimes impose enforceable obligations on those who prescribe or use medicinal products. In the case of veterinary medicinal products, the review of RMM performed by the CVMP led to a determination of the characteristics RMM should have in order to ensure greater compliance on the part of prescribers and users[191].

An example of good practice in this regard is the case of Sweden, where a risk classification system was put in place, which allows prescribers to have a clear idea of whether a medicinal product is harmful to the environment (whether it was authorised prior to or after 30 October 2005). This classification allows for a ranking of medicinal products, based on their potential risk to the environment (i.e. the PEC/PNEC results): they are ranked as products with insignificant (PEC/PNEC ≤ 0.1), low (0.1 < PEC/PNEC ≤ 1.0), moderate (1.0 < PEC/PNEC ≤ 10) or high environmental risk (PEC/PNEC > 10). A classification was also adopted regarding biodegradation and bioaccumulation of medicinal products in the environment (FASS , 2007) (LIF, 2010).

In addition, the legislation on medicinal products does not give the EU competence to influence prescribability of authorised products in MS; this is a competence of MS[192].

8.1.4 Comparison of EU legislation on MA process for medicinal products for human and veterinary use

Table 3 below allows for a comparison of EU legislation (taking into account the ERA guidelines drafted by EMA) on the MA process applicable to human medicinal products (HMP) and the one applicable to veterinary medicinal products (VMP). This comparison focuses on ERA and RMM.

[190] CVMP Reflection paper (EMA, 2012c), supra, p.4.

[191] CVMP Reflection paper (EMA, 2012c), supra, p.10. The necessary characteristics of RMM identified by the CVMP (in addition to fulfilling the VICH-TGD criteria) are the following: - the potential risk to the environment is clear; - the recommended measure to mitigate the risk is specific and clear; - the recommended measure can be readily/easily implemented; - the measure is under the direct control of the animal owner/prescriber (that is, not relying on a third party for implementation); - the measure does not require the animal owner/prescriber to make a direct choice between the appropriate treatment for a specific indication and protection of the environment.

[192] Based on information provided by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study

Table 3: Comparative table of EU legislation on MA process for HMP and VMP

ERA – current EMA guidelines	CHMP guideline on ERA of HMP	-VICH guideline 6 (GL6) for Phase I (EMA, 2000); -VICH guideline 38 (GL38) for Phase II (EMA, 2004); -CVMP Guideline on environmental impact assessment for VMPs in support of VICH guidelines GL 6 and GL38 (VICH-TGD) (EMA, 2007).
ERA – medicinal products for which it is required	-MA applications for new HMP; submitted after 30 October 2005 -Type II variations if increase in the environmental exposure; -Extension applications if potential increase in environmental exposure; -Generics.	-New VMP; -Type II variations; -Extensions; -Generics; -Etc.
ERA – medicinal products for which an ERA is not required	-Authorisation renewals; -Type IA and IB variations; -Substances such as vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines and herbal products	Phase I (GL6) excludes a certain number of products from really having to perform an ERA (if answer is 'no' to certain questions of the decision tree): -Electrolytes, peptides, proteins, vitamins, and other compounds that occur naturally in the environment; -Medicines for pet (non-food animals); -Medicines intended for use in a minor species that is reared and treated similarly to a major species for which an ERA already exists; -Medicines used to treat a small number of animals within a flock or herd.
ERA – scientific requirements (guidelines)	Tiered assessment: -Phase I: Assessment of environmental exposure (based mainly on PEC); -Phase II: Environmental fate and effect analysis: -Tier A: Initial environmental risk assessment, involving the calculation of a risk quotient –RQ– (PEC/PNEC); - Tier B: Refinement of risk quotient + possible RMM.	

	Phase I: -PBT assessment mandatory -Based only on medicinal product substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion; -Screening for PBT for medicinal product substances with a log Kow >4.5; -Calculation of PEC in surface water – action limit value: 0.01 µg/L. Phase II: -Required if PECsurfacewater ≥0.01 µg/L; -Required for medicinal product substances that may affect reproduction of vertebrate or lower animals at concentrations lower than 0.01 µg/L; -Tier B in most cases where risk quotient (PEC/PNEC) > 1 (but > 0.1 if PEC (microorganisms).	Phase I: -Application of decision tree -EICaquatic action limit value: 1 µg/L (for aquatic species) -PECsoil action limit value: 100 µg/Kg (for terrestrial species) Phase II: -Required if EICaquatic > 1µg/L; -Required if PECsoil > 100 µg/Kg; -Always required for compounds known to be active at very low concentrations; -PBT assessment -Distinction between 3 branches: Aquaculture Intensively reared animals Pasture animals -Tier B if refined RQ > 1.
ERA results – Impact in MA process	Not part of the benefit-risk analysis	Part of the benefit-risk analysis
ERA – availability of data and results	-Environmental data and ERA results are not mentioned in the directives as having to be included in the assessment report and/or made publicly available; but -Some information on ERA results may be found in EPARs (or in some national PARs), after deletion of commercial confidential information; -ERA data considered as 'commercial confidential information'	
RMM	Imposed when still environmental risks at the end of Phase II Tier B:	
	-Indication of potential risks in the documents communicated to the public (package leaflet – PL) -Product labelling, SPC, PL for patient use, product storage and disposal	-ERA must identify any precautionary measures, which may be necessary to reduce the risks to the environment; -Veterinary prescription if special precautions required; -RMM possible in SPC and product literature (PL and product labelling).

8.1.5 Section Summary

8.1.5.1 Marketing authorisation (MA) process

- Under the centralised procedure, only the CVMP has a member appointed specifically due to his expertise on environmental risk assessment. The CHMP does not include any environmental expert;
- Not all MS have experts with enough ERA experience to perform it;

- The level of requirements may vary from one MS to another, and parallel procedures for the same product can be followed in different (critical versus less critical) countries. This may give rise to a form of forum shopping for the granting of a MA. The decentralised and mutual recognition procedures may therefore often lead to different assessments of the same APIs in different products and in different MS, but also in the same MS; and
- The ERA results for **medicinal products for human use** do not play a role in the granting of the MA, as they are not included in the risk/benefit analysis, whereas the ERA results for **veterinary medicinal products** are included in the risk/benefit analysis. RMM may be required based on the ERA results and are then a part of the MA process. However, the efficiency of RMMs is not evaluated, the diminution of the risk is not measures and thus not properly considered in the benefits-risks analysis.

8.1.5.2 Environmental Risk Assessment (ERA)

Medicinal products for which an ERA is required

- There is a lack of ERA for most **human medicinal products**, as numerous active pharmaceutical ingredients contained in such medicinal products were authorised prior to 30 October 2005, when performing an ERA (and not only providing an indication of potential environmental risks) became an obligation for new medicinal products. The potential environmental risks they may pose to the environment is therefore not assessed. In addition, an ERA is requires for type II variations (when an increase in environmental exposure is expected), extension applications and generics;
- For **veterinary medicinal products**, an ERA is required for all types of MA applications, including for new medicinal products, generics, type II variations `and extensions. However, application of the Phase I decision tree entails that the following veterinary medicinal products, among others, do not actually require environmental information for the ERA: medicinal products for pets, medicinal products intended for use in a minor species that is reared similarly to a major species for which an ERA already exists, and medicinal products used to treat a small number of animals within a flock or herd;
- ERA guidelines, whether for medicinal products for human or veterinary use, narrow the scope of medicinal products for which an effective ERA is required. It results from the applicable guidelines that in practice environmental information is not required for a certain number of products. Although, for instance, Phase I decision tree applicable to veterinary medicinal products is technically part of the ERA, it implies that environmental information end up not being required for certain veterinary medicinal products;
- An ERA is required for every medicinal product to be put on the market although the actual assessment concerns the active pharmaceutical ingredient. Since ERA information is deemed confidential, data cannot be reused from a dossier to

another, even if the medicinal products concerned contain the same active substance. This means that ERA results may be based on different endpoints and may therefore differ from a product to another. Furthermore, since the ERA is based on a single product only, it does not account for the whole API environmental loads originated by the different products. In addition, if a competent authority knows from other MA applications that an active pharmaceutical ingredient has a lack of environmental risk, the dossier must still be complete and include the ERA, with a repetition of previous studies; and

- Lack of dossier completeness introduces economic issues: for instance, under the decentralised procedure a MS acting as RMS could require the submission of a full dossier from one MA applicant, whereas another MS (also acting as RMS, but in another procedure) could accept a dossier with only endpoints from another applicant. In such a case, the time and costs borne by these applicants will greatly vary.

ERA guidelines: scientific requirements

- Not all medicinal products undergo a thorough environmental risk assessment as some stop at Phase I because of the action limit applied. For thosemedicinal products, the environmental properties are therefore still unknown;
- Scientific robustness of ERA is still debated, in particular the relevance of the action limit values set in the ERA guidelines should the effect of mixtures be considered beyond the effect of single substances, and the use of endpoints failing at reflecting medical products' specificities. It is difficult to assess the effectiveness of these limit values to protect the environment for all pharmaceutical substances because the knowledge for the hazard characterisation is often lacking.

- The ERA for **medicinal products for human use** does not take into account metabolites for calculation of the PEC. Metabolites are taken into account only when a Phase II – Tier B is performed. For **veterinary medicinal products**, metabolism and excretion data are taken into account only if the PEC requires refinement in Phase II – Tier A;
- A PBT assessment is or may be required as part of the ERA, depending on whether the assessment concerns human medicinal products or veterinary medicinal products ;;
- Regarding PBT, a PBT screening should always be performed for human medicinal products and, if considered, relevant also a further assessment should be performed according to REACH guidance on PBT, regardless of whether the substances' environmental concentrations meet the trigger value under Phase I. On the contrary, for veterinary medicinal products, a PBT/vPvB assessment must only be performed during Phase II of the ERA, and therefore depends on whether the substance met trigger values under Phase I (in terms of environmental

concentrations). Moreover, no specific guidance is available on how to include this PBT assessment in the risk-benefit analysis or on which risk management measures would be needed in order to grant the MA for a veterinary pharmaceutical presenting PBT properties;

- There is a lack of consistency regarding ERAs performed within the EU for products with the same active pharmaceutical ingredient (whether for **human** or **veterinary medicinal products**): compliance with and interpretation of ERA guidelines is indeed not uniform in the various MS, although consistency of ERA data has improved; and
- In case of disagreement between MS on the results/procedures for the ERA (under the decentralised and mutual recognition procedures), a referral procedure exists before the EMA.

Impacts of the ERA results in the MA process

- A MA may be refused on environmental grounds for medicinal products for veterinary use, but not for those for human use. In particular, the results of the PBT assessment have up to now no consequences on MA for human medicinal products. Thus, even if the results of the ERA highlight the environmental risk and PBT status of a substance, it is unclear which policy can be followed to manage human medicinal products with proven PBT or vPvB properties;
- There have been refusal of MA for **veterinary medicinal products** based on the ERA under the decentralised and mutual recognition procedures;
- There are sometimes data gaps in the ERA presented for **veterinary medicinal products**, which can be partially linked to the complexity and lack of knowledge regarding ecological effects (see sections 5.1 and 5.2), and CVMP must then take a decision based on the presented material. Although timelines for assessment of medicinal products are well defined in law and it assumes that the dossier submitted is complete, in practice MS may reportedly require that additional data be submitted, but time constraints may impede it; and
- There may also be data gaps regarding ERA submitted for **medicinal products for human use**: the ERA may be incomplete or altogether absent from the MA application (in Germany, for **about 60%** of medicinal products the ERA could not be finalised and for the Top 10 human medicinal products found in surface water not a single ERA was available (UBA, 2010)). The MA is therefore granted with "post-marketing commitments". However, companies are not obliged to submit this data as the ERA is not included in the risk/benefit balance.

Availability of ERA data and results

- Environmental datasets produced for medicinal products are usually not publicly available: their accessibility is generally limited to risk assessors only;
- EMA and national competent authorities invoke confidentiality reasons to justify the absence of publication of the environmental data itself; and

- ERA endpoints are not always published: publication generally depends on the type of procedure and the RMS (for decentralised and mutual recognition procedures). However, even when published, the ERA endpoints may be hard to find.

8.1.5.3 Risk Mitigation Measures (RMM) and pharmacovigilance

- Although the authorisation holder must include RMM in the product information when a risk to the environment exists (whether for **human** or **veterinary medicinal products**), these RMM are only recommendations and compliance with RMM has therefore only a voluntary character;
- Not all RMM may be readily or easily complied with by prescribers or users, in particular concerning **veterinary medicinal products**. They could nonetheless have an educational role for prescribers;
- EU legislation does not provide any obligation to carry out monitoring of environmental risks once the authorisation is delivered, or pursuant to a decision to withdraw or modify RMM;
- In the case of **veterinary medicinal products,** information on potential environmental problems must be taken into account in the pharmacovigilance system. However, this is reportedly neither fulfilled nor controlled. For **human medicinal products**, although the emerging environmental problem related to the presence of medicinal product residues in waters and soils is acknowledged, there is no obligation to collect and report information on environmental risks as part of the pharmacovigilance systems. Nonetheless, a MS may suspend the use in its territory of a **medicinal product for human or veterinary use**, if urgent action is essential to protect human health or the environment;
- Prescribing physicians may lack guidance or knowledge to promote medicinal products less harmful to the environment. The risk classification system implemented in Sweden is an example of good practice in this regard; and
- The EU legislation on medicinal products does not include provisions on the prescribability of authorised medicinal products; this is a competence of MS.

8.2 Common findings of case studies

Seven case studies of active pharmaceutical substances used in medicinal products for both humans and animals were carried out in order to identify, support and illustrate legislative factors of influence identified in section 8.1. The APIs of interest were selected in agreement with the EAHC.

The detailed case studies are provided in Annex 3 to the present study. They illustrate scientific characteristics and procedural information, notably on market authorisation procedure, regarding each of the studied APIs.

It results from investigations and interviews carried out as part of these case studies that the findings on procedural aspects of the medicinal products identified are similar. This section therefore aims to present general findings applicable to the seven above-mentioned active pharmaceutical ingredients. Scientific aspects of the case studies are presented in Annex 3.

Interviews with various national regulatory agencies and information search carried out have revealed certain similarities in procedural aspects in various MS, but also discrepancies that should be highlighted. Some of these findings echo certain shortcomings identified in section 8.1 above. These findings apply to both human and veterinary medicinal products, unless otherwise indicated.

8.2.1 General aspects

- **Handling of marketing authorisation (MA) applications**

Very few medicinal products go through the national procedure as the majority goes through the decentralised or mutual recognition procedure. In addition, for the active substances studied for veterinary medicinal products, the vast majority of MA applications are for generics, as these substances have been on the market for many years (at least 15 years).

Under the decentralised and mutual recognition procedures, there are interactions between the RMS and CMS at all stages of the assessment, and the CMS provide feedback and comments on the assessment and the conclusions. In case of disagreement and pursuant to the EU medicines legislation, the CMS will state its objection to the RMS. Exchanges will take place within a specific timeframe (depending on the considered procedure), and will be between the CMS (it will state the additional elements it requires from the MA applicant), the applicant (who presents its case) and the RMS (which comments on the acceptability of the applicant's response). If the disagreement persists at the end of this timeframe, the case will be referred to CVMP or CHMP by the RMS.

There are also differences in the way MS handle MA applications, especially regarding the evaluation of the environmental risk assessment (ERA) submitted by the MA applicant. This evaluation is done by in-house experts in some national regulatory agencies, whereas in other countries the evaluation may be externalised to other national agencies, such as the authority in charge of environmental matters or in special cases to experts who work in research institutes.

- **Resources for the evaluation of the ERA**

Not all national regulatory agencies include an ecotoxicologist. In the case of veterinary medicinal products, this is an important issue as the ERA results are included in the risk/benefit analysis. One interviewed national regulatory agency, which does not include an ecotoxicology, indicated that the evaluation of the ERA is undertaken by reviewing the data and determining if they are in compliance with CVMP guidelines, which may lead to the ERA data being considered acceptable («acceptability of the data») as to the highlighting of obvious deficiencies. This lack of resources may also be problematic for procedures involving CVMP (centralised procedure or referrals), as the CVMP often relies on national experts (and sometimes on the members of the working party or the environmental risk assessor), which can be problematic in countries where there are no expert ecotoxicologists.

However, according to some competent authorities, where a national regulatory agency does not include an environmental risk assessor (ecotoxicologist), it is unlikely that this agency would act as lead authority on new molecules. The national authority therefore could potentially refuse to act as RMS in the case of a decentralised procedure (but could not do so in the case of a mutual recognition procedure, as this procedure applies when a medicinal product has already received a MA in the RMS). However, other CAs highlighted that national authorities receive some money to act as RMS and this could act as a trigger to accept the task.

8.2.2 Requirement of an ERA for generics

The requirement that an ERA has to be performed for generic medicinal products differs depending on the type of medicinal product involved, i.e. for human or veterinary use.

- **For medicinal products for human use**

National regulatory agencies, and hence MS, tend to differ as to whether an ERA is required for generic medicinal products. Based on the CHMP guideline on ERA of medicinal products for human use, some MS do not require that an ERA be submitted when there is no increase of the environmental exposure to the active pharmaceutical ingredient: this absence of increase is viewed as a suitable justification not to require an ERA. Thus, in such a case a MA applicant must either submit an ERA or provide a rationale for not doing so.

- **For medicinal products for veterinary use**

Since 2005, submission of an ERA is required for generics (they must provide a full dossier, including ecotoxicological studies). For certain active substances, this has led to an evolution of the assessment of the environmental risk. An example of such an evolution is provided with Ivermectin as: (i) all original MA where granted when no ERA was required, (ii) when performing an ERA became a requirement, it was applicable to new medicinal products and not to generics (before 2005), and (iii) performing an ERA became an obligation applicable to all generics from 2005 onward. This change in requirement explains the denial of MA for the medicinal product 'Pharmasin 100% W/W Water Soluble Granules', as the requirement that an ERA be submitted for generics came into force when the MA application was already pending: the initial MA therefore was denied only on the grounds that the dossier was incomplete as it did not contain an ERA; a new MA application was later submitted, including an ERA, and authorisation was granted.

For active substances that have been on the market for a long time, MA applicants can be quite reluctant to provide an exhaustive ERA, especially for generics, as they consider that products containing this active substance have been on the market for a long time (for more than 15 years) and thus do not present a risk to the environment. However, the MA application for a generic is often the first time an ERA involving this specific active substance will be undertaken.

8.2.3 Evaluation of the ERA

- **Quality and completeness of the ERA**

The absence of an ERA is generally seen as a deficiency, as the submission of an ERA is a legal requirement. However, when an ERA is provided, the problem is sometimes that the ERA submitted is still deficient or insufficient.

For many medicinal products, the evaluation of the ERA is carried out rapidly as many conclude to a lack of exposure. However, if the ecotoxicological dossier appears incomplete (especially for types of medicinal products which must automatically undergo a Phase II, such as antiparasitic medicinal products), questions will be sent to the MA applicant. Exchanges take place between the regulatory agency and the MA applicant: if the procedure results in disagreement, a referral may be launched. It has nonetheless been reported that it has become a recurrent practice in the MA procedure to decrease potential environmental risks through a variety of refinement steps while performing an ERA, by notably using lower PECs, dilution of manure, decreased percentage of treated animals, etc. Through such practice, the ERA could conclude that there is no environmental risk: the regulatory agency would therefore not have to perform the risk-benefit analysis and the MA could be granted.

Furthermore, it appears that in some cases, whether under the decentralised and mutual recognition procedures (and even in case of referrals), when an ERA is not complete (e.g. not all required studies are provided) but the ecotoxicological studies submitted already conclude to the existence of environmental risks, the missing studies are not always requested to the MA applicant and risk mitigation measures (RMM) will be imposed on the basis of the existing studies. In addition, it has been reported that in the case of referrals, the CVMP may decide, based on the information available, that a risk is not likely and thus consider that the studies do not need to be provided (despite the fact that the dossier should be complete). In the first situation, some MA applicants reportedly tend now to refer to the outcome of past procedures, notwithstanding the fact that it does not necessarily involve the same active substance, and consider that they should not have to submit a full dossier but could only state that there is an environmental risk and include RMM in the summary of products characteristics. This rationale has reportedly been approved by a number of countries and has not been questioned by the CVMP, as the CVMP has not been requested to address this issue thus far.

Finally, how incomplete dossiers are handled throughout the MS may create economic inequalities, as MA applicants submitting a full dossier would incur much higher costs than those submitting only endpoints (which is sometimes accepted by some MS, although not legally allowed).

- **Critical review and outcome of the ERA**

National regulatory agencies confirmed that ERA results may vary for the same active substance, as the ERA for each MA application must be evaluated on its merits (i.e. what is contained in the MA application), not taking into account results obtained through other procedures or means. Various agencies view this as a problematic issue as they consider that the information included in the ERA should include either studies performed for the MA applicant by a commercial laboratory, or all published literature, and not only the studies that are beneficial to the MA applicant. Some nevertheless indicated that they look for information in the dossier but also at other information in the public domain and, if a specific issue is thus revealed, they may send questions to the applicant in order e.g. to ask for additional information or require additional data or an expert comment. This can also lead to the strange situation in which, because of

deficiencies in the fate studies, one MA applicant performs the ERA for the parent compound, while other MA applicants have performed the ERA for the more environmentally relevant metabolite.

Moreover, it would appear that some MA applicants sometimes try to avoid review of the ERA by critical national regulatory agencies. This may even lead to distinct MA procedures being launched in different MS for the same medicinal product.

In addition, some MS acting as CMS often rely on other national agencies to critically review and assess the RMS report, although these other agencies may not always be involved in the MA procedure as CMS (and as a result, no CMS critically reviews the report). It also was pointed out that many CMS tend to simply rely and take for granted the findings of the RMS report, with the result that they sometimes fail to critically assess such report by submitting it to an expert ecotoxicologist.

In the case of the centralised procedure for veterinary medicinal products, the CVMP may draw its conclusions regarding the ERA based on recommendations of the ERA working party. However, it does not always do so.

Finally, many medicinal products do not often undergo a thorough ERA as they may be exempted from such a requirement (e.g. application of the Phase I decision tree to veterinary medicinal products, see section 8.1.2) or they are below the action limit value.

- **Time constraints**

A national regulatory agency reported that the conclusions of the ERA generally opposed the MA procedure timeframe, whether because of procedural time constraints or because of the goal (notably on the MA applicant's part) to obtain the MA in the briefest time-period in order to market the medicinal product as soon as possible, Such a situation may lead to cases where, for instance, RMM are already discussed and imposed although the ERA is not yet finalised in light of the applicable guidelines (e.g. the Tier B assessment is not possible).

8.2.4 Availability of ERA results

- **Summary of Products Characteristics (SPC)**

The national regulatory agencies interviewed all indicated that they publish on their website the SPC. For some, such publication is an ongoing process, as old medicinal products did not necessarily have SPC before.

- **Publication of Public Assessment Reports**

As to the publication of public assessment reports (PAR), those are not always available on the national regulatory agencies' websites. For one national authority, this is an ongoing improvement process, but without any retroactive effect: no PAR will be published for those medicinal products for which no such report was drafted at the time the MA was granted.

When PARs are available on websites, they are usually so only for those medicinal products for which the MS acted as RMS under the decentralised or mutual recognition procedures, or when the MA procedure followed was national. PARs will thus not be generally available on national

authorities' websites, for those medicinal products for which the national agency acted only as CMS, notwithstanding the fact that the MA was ultimately granted in this MS. However, best practices exist: one national agency undertakes to publish, in addition to PARs for which they act as RMS, some PARs drafted by other agencies for medicinal products for which the CA acted as CMS. In addition, within a MS, differences may exist; for instance, PARs for human medicinal products are published and for veterinary medicinal products they are not.

In addition, MS usually have the same template for PARs, as the assessment is structured in a way that follows the same layouts as the MA dossier, which explains why it is quite similar in different national regulatory agencies.

However, the possibility for consumers to obtain information on a particular active substance faces several challenges, notably:

- Not all national agencies' websites allow for a search by active substance: some only give the possibility to search by name of medicinal product;
- The name of a medicinal product may vary from one MS to another: it might therefore be impossible (or at least extremely difficult) for consumers to have access to the relevant PAR (e.g. when «his» MS acted only as CMS, and the medicinal product has a different name in the MS which acted as RMS and published the PAR).

Information contained in PARs

The information contained in PARs is usually quite succinct, indicating only (i) whether the ERA stopped at Phase I, and (ii) in case of a Phase II, whether the outcome was favourable (no risks) or whether RMM were imposed.

This lack of information results from the fact that the studies carried out by pharmaceutical firms for the ERA are the property of these firms (MA holders do not want these data to fall in the public domain, so as to avoid them being used by competitors, notably for MA application for generics). Several national regulatory agencies indicated that, due to the commercially sensitive nature of this information, draft PARs are sent to the MA applicant/holder before they are made available to the public.

Availability of ERA results for other national agencies

Some national agencies may communicate confidential data contained in the ERA to other agencies, such as the agency in charge of human/veterinary medicinal products (when it is not a 'mixed' agency), or water agencies for the purpose notably of conducting monitoring investigations, etc. However, the information is not voluntarily provided to an external agency such as water agencies: the competent authority awaits official requests (e.g. for prioritisation of molecules) and, when providing the ERA data, clearly indicate that the information is owned by a third party and therefore confidential. Should the agency to which the information is communicated wish to publish the data, it first will have to obtain the authorisation of the pharmaceutical company, which owns said data. However, in principle, the endpoint data is not confidential and should be available even if not all national authorities make it available and even if they do, it is often hard to find. Such exchanges between national medicines authorities and other agencies do not take place in all MS.

8.3 Other EU legislation relevant to the issue of medicinal residues in the environment

8.3.1 Good Manufacturing Practices

The EU provides guidance on the manufacturing of medicinal products for human and veterinary use through principles and guidelines of Good Manufacturing Practice (GMP). The EU GMP guidelines are based on the guidelines developed at international level by the World Health Organisation (WHO), which are soon to be updated.

The GMP is primarily concerned with ensuring quality of the medicinal products manufactured. In the EU, these principles and guidelines are set out in two directives: Directive 2003/94/EC (which replaced Directive 91/356/EC) on medicinal products for human use[193], and Directive 91/412/EC on veterinary medicinal products[194]. Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use[195].

Directives 2001/83/EC (medicinal products for human use) and 2001/82/EC (veterinary medicinal products) make specific reference to GMP, as the manufacturer of medicinal products is subject to the holding of a manufacturing authorisation[196] and is obliged, in this regard, to comply with the principles and the guidelines of GMP for medicinal products and to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on GMP for starting materials[197].

However, none of the documents applicable to GMP (directives and guidelines) mentions the risk that production of medicinal products may pose to the environment: the guidelines specifically state that GMP does not cover aspects of protection of the environment[198]. As such, environmental concerns are therefore not taken into account at the manufacturing stage under GMP (see also specific section on IED). The necessity to take into account the environmental risks related to the manufacturing of medicinal products was however raised by some MS, in particular Sweden, where the Swedish government requested the Swedish Medical Products Agency to act internationally for a change of GMP in order to include emissions to the environment resulting from the manufacturing of medicinal products. Although this initiative has not yielded any tangible results thus far, the Swedish government has put forward the issue in a European

[193] Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of pharmaceuticals for human use and investigational pharmaceuticals for human use. It replaced Directive 91/356/EEC to cover good manufacturing practice of investigational pharmaceuticals.
[194] Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary pharmaceuticals.
[195] EU Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use, Doc. Ref. SANCO/C8/AM/sl/ares(2010)1064597, last updated December 2010. See EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, available at ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
[196] Article 40 of Directive 2001/83/EC, supra, and Article 44 of Directive 2001/82/EC, supra.
[197] Article 46(f) of Directive 2001/83/EC, supra, and Article 50(f) of Directive 2001/82/EC, supra. The 'basic requirements for active substances used as starting materials' are included in Part II of the GMP Guidelines, supra.
[198] See EU Guidelines on GMP, supra, and more particularly § 1.1 of Part II: Basic Requirements for Active Substances used as Starting Materials.

Council meeting on minister level, where it was apparently mentioned as a question to keep under surveillance in the future[199].

8.3.2 REACH

Regulation (EC) 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)[200] lays down provisions for the manufacture, placing on the market of chemical substances (certain provisions apply to preparations and articles), with the purpose of improving protection of human health and the environment from the risks of chemicals. However, medicinal products are partially exempted from REACH, as the regulation contains specific provisions aiming at avoiding double regulation. These include, as noted in particular by an external consultant in a report ordered by the European Commission that identifies potential gaps or overlaps with other EU legislation (Milieu, 2012):

- Exemptions of substances from the REACH requirements (Titles II, V, VI and VII) regarding registration, downstream users, evaluation and authorisation so far as they are used in medicinal products[201]. The European Chemical Agency (ECHA) has published guidance on registration, which provides that both active substances and excipients are exempted from registration, insofar as they are used in medicinal products (substances used in non-medicinal mixtures will be subject to the REACH registration provisions)[202] (ECHA, 2012);
- Exemptions of medicinal products in their finished state from the REACH requirements (Title IV) for information (Safety Data Sheet) in the supply chain[203]. Note, however, that this exemption applies only to preparations; substances in bulk form intended for use in medicinal products are not exempted from the information in the supply chain requirements;
- Medicinal products are not exempted from Title VIII of REACH on restrictions on the manufacturing, placing on the market and use of certain dangerous substances and preparations. Restrictions are contained in Annex XVII and medicinal products must therefore comply with restrictions, which could be imposed on active pharmaceutical ingredients. There are derogations for medicinal products from the restrictions applicable to the use and placing on the market of carcinogenic, mutagenic and reprotoxic (CMR) substances as

[199] Answer to a questionnaire, provided by Åke Wennmalm, from SustainPharma (answer received on 2 January and 15 February 2013), in the context of the stakeholders' consultation carried out by BIOIS for the present study. This interview provided information that would be hardly accessible otherwise.
[200] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.
[201] Article 2(5)(a) of the REACH Regulation, supra, which specifically mentions Regulation (EC) No 726/2004, Directive 2001/82/EC and Directive 2001/83/EC.
[202] (ECHA, 2012) provides: "The exemption does not distinguish between active or non-active ingredients as it applies to any substance 'used in medicinal products'. Excipients used in medicinal products are therefore also exempted from registration. Note that quantities of the same substance used for other uses than pharmaceuticals are not exempted. Only the quantities of the substance used in medicinal products are exempted from the registration obligation" (p.31).
203 Article 2(6)(a) of the REACH Regulation, supra.

substances or in mixtures for supply to the general public[204]. REACH does not however include general provisions regarding the manufacturing of active pharmaceutical ingredients, but restrictions could target active pharmaceutical ingredients, but also the manufacturing process itself[205].

REACH specifically requires information on environmental hazards at all stages of the life cycle. The fact that medicinal products are exempted from several Titles of REACH covering possible risks related to the manufacturing of substances used in medicinal products (although, theoretically, Annex XVII could cover all active pharmaceutical ingredients), and that the legislation on medicinal products does not cover these risks, may be viewed as a gap (Milieu, 2012). Indeed, according to one national agency, the ERA guidelines do not address the environmental exposure in relation to the manufacturing or distribution of medicinal products, but address such exposure only concerning consumption and excretion of medicinal products and residues[206].

8.3.3 Monitoring and controls under the Industrial Emissions Directive (IED)

- **Monitoring and controls at the manufacturing stage**

Industrial facilities at which pharmaceutical products, including intermediates, are manufactured (production, formulation, and conditioning) are covered by the Industrial Emissions Directive (IED, 2010/75/EU)[207] which, among other things, requires them to monitor and control emissions of polluting substances. However, special provisions for installations and activities using organic solvents, which include plants manufacturing pharmaceutical products (IED, Chapter 5 and Annex VII, part 1(8)), may not apply to small and medium, because of the application of consumption thresholds (IED, Annex VII, part 2(20)). In any case, these special provisions apply only to the use of organic solvents.

The IED also provides that MS must ensure that the permit delivered pursuant to the Directive (and therefore the transposing legislation) includes measures such as "*emission limit values for polluting substances listed in Annex II, and for other polluting substances, which are likely to be emitted from the installation concerned in significant quantities, having regard to their nature and their potential to transfer pollution from one medium to another*"[208].

Annex II of the IED does not yet specifically include any active pharmaceutical ingredients in the list of polluting substances in the air and water, for which emission limit values should be set and monitoring carried out. There are therefore no specific controls requirements for emissions of individual pharmaceutical substances from the pharmaceutical industry (and national legislation

[204] Entries 28 through 30 of Annex XVII to REACH, supra.
[205] See notably REACH, supra, Article 68.
[206] Based on information provided by the Federal Agency for Medicines and Health Products (FAMHP) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[207] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (IED). See Article 10 and Annex I, clause 4.5 of the IED. The IED (see art.81) will repeal, with effect from 7 January 2014, Directive 2008/1/EC of the European Parliament and of the Council of 15 January 2008 concerning integrated pollution prevention and control (IPPC).
[208] IED, Article 14(1)(a).

does not seem to include such emission limit values[209]). However, active pharmaceutical ingredients could potentially fall within two substance groups listed in Annex II in relation to water pollutants. Those substance groups are:

- substances and mixtures which have been proved to possess carcinogenic or mutagenic properties or properties which may affect reproduction in or via the aquatic environment (water pollutants, point 4), and
- persistent hydrocarbons and persistent and bioaccumulable organic toxic substances (water pollutants, point 5).

In addition, Annex II mentions, regarding water pollutants, "substances listed in Annex X to Directive 2000/60/EC", i.e. the list of priority substances set forth in the Water Framework Directive (WFD). This list, as established by the Environmental Quality Standards Directive (EQSD, 2008/105/EC), is meant to be revised every four years. However, following negotiations on the Commission's 2012 proposal led in April 2013, the revised list of priority substances will not include any active pharmaceutical ingredients, but three such products will be included on a watch list (see section 8.3.5 on water legislation). Should active pharmaceutical ingredients be included in the list of priority substances in the future, emission limit values would be established and pharmaceutical plants would be required to monitor and control the emissions of said APIs into water.

Independently from Annex II, there are some governing principles that apply to industrial facilities covered by the IED (including production of pharmaceutical products including intermediates). General principles governing the basic obligations of the operator include notably that all the appropriate preventive measures are taken against pollution, and that no significant pollution is caused (IED, Article 11 (a) and (c)). The permit delivered to operators of such facilities must include all measures necessary to comply with these requirements (IED, Article 14).

The permit conditions, including emission limit values, must be based on the Best Available Techniques (BAT)[210]. However, BAT includes both the technology used and the way in which the installation is designed, built, maintained, operated and decommissioned (Article 3(10)(a)), and is therefore not limited to establishing associated emission levels. BAT conclusions and BAT Reference Documents (BREFs) are adopted and published by the European Commission[211]. BREFs may refer to active pharmaceutical ingredients, but do not recommend any associated emission levels (BREF, 2006). However, the installations still need to apply BAT.

To this day, there are no relevant data on the actual level of emission of active substances from plants manufacturing medicinal products, and level of such substances passing through wastewater treatment plants.

However, Directive 2013/39/EU placed three active pharmaceutical ingredients on the first watch list, which entails the obligation for Members States to monitor these substances at least annually for up to four years; some data may thus start being accessible, at the national but also

[209] Based on information provided by SustainPharma (Sweden), RIVM (the Netherlands) and UBA (Germany), in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[210] IED, Article 14(3): "BAT conclusions shall be the reference for setting the permit conditions".
[211] Pursuant to IED Article 13 'BAT reference documents and exchange of information'.

at the EU level. Indeed, the EU established a publicly accessible electronic database: the European Pollutant Release and Transfer Register (E-PRTR)[212], which includes information reported by operators of pharmaceutical manufacturing plants to its competent authority[213], such as emissions of organic solvents used at pharmaceutical plants[214]. However, active pharmaceutical ingredients do not appear in the list of pollutants for which information must be provided[215]. Nonetheless, the E-PRTR Regulation requires the Commission, assisted by the European Environment Agency, to include in the E-PRTR information on releases from diffuse sources, where such information exists and has already been reported by MS[216]. Such information could include data on medicinal products.

- **Monitoring and controls in agriculture and farming**

The IED provisions mentioned above as applying to plants manufacturing medicinal products also apply to the intensive rearing of poultry and pigs[217].

As to BAT, the BREF note under the IPPC Directive (96/61/EC) relating to the rearing of poultry and pigs mentions the entry of residues of veterinary medicinal products into soil and groundwater only in passing. Whilst it comments that antibiotics, metabolics and other medicinal products can be emitted to soil and groundwater from intensive livestock production systems, it states that the focus has been on the emission of nitrogen and phosphorus (BREF, 2003).

The BREF note acknowledges that the environmental effects of antimicrobials are unknown, such as the development of resistance to antibiotics in soil and water, the consequences for soil and water ecology, and other environmental effects (BREF, 2003). Whilst it states that the most common hazardous residues result "*from medicines that have been used or are past their expiring date*", the focus of the discussion on the on-site disposal of residues is stockpiling, burning, burying and re-using, and not residues from veterinary medicines that directly enter soil and groundwater from pigs and poultry (BREF, 2003). A draft BREF note to supersede the above version, dated March 2011, does not include any significant change on these issues (BREF, 2011).

8.3.4 Monitoring and controls in agriculture and farming under the Sewage Sludge Directive

The Sewage Sludge Directive (86/278/EEC)[218] aims to regulate the use of sewage sludge in agriculture in order to prevent harmful effects on soil, vegetation, animals and man, thereby encouraging the correct use of sewage sludge[219]. Although the Directive protects soil quality, it mostly focuses on limit values for heavy metals but does not refer to residues of medicinal products.

[212] Regulation (EC) No 166/2006 of the European Parliament and of the Council of 18 January 2006 concerning the establishment of a European Pollutant Release and Transfer Register and amending Council Directives 91/689/EEC and 96/61/EC.
[213] See Article 5 and Annex I to Regulation (EC) No 166/2006, supra.
[214] See Annex VII of the IED, supra.
[215] Annex II to Regulation (EC) No 166/2006, supra.
[216] Article 8(1) of Regulation (EC) No 166/2006, supra.
[217] IED, Annex I, clause 6.6.
[218] 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.
[219] Article 1 of the Sewage Sludge Directive.

Despite the fact that sewage sludge is largely used in certain MS (e.g. France) as fertilisers in agriculture, the Directive does not require the amount of medicinal products residues present in sewage sludge to be monitored or regulated. Medicinal products, including antibiotics, may thus be present in the sludge from which it may enter soil, sediments in surface waters and groundwater (Kümmerer, 2004).

Some German Länder, such as Bavaria and Nordrhein-Westphalia, thus chose to pass legislation restricting the use of sewage sludge in agriculture, one of the reasons for this being the environmental risks posed by the presence of medicinal products in sewage sludge (Roig, 2010). However, national legislation does not generally require monitoring of pharmaceutical residues in sewage sludge[220].

8.3.5 Water legislation

- **Water Framework Directive and daughter Directives**

The general EU framework for water consists of the Water Framework Directive[221] and its daughter Directives: the Environmental Quality Standards Directive (EQSD)[222] and the Groundwater Directive (GWD)[223]. The environmental aim of the Water Framework Directive is to achieve good chemical and ecological status of water bodies within the EU by 2015. The good status of waters must be reinforced through specific measures.

The Water Framework Directive potentially provides an adequate framework to deal with chemical pollution affecting water; however, it does not specifically target medicinal products (Keessen, 2012) any more than any other group of substances. Substances present on a priority list and other specific pollutants discharged in substantial volumes into water bodies must be monitored and progressively reduced. Annex X of the Water Framework Directive, as amended by the EQSD, currently contains 33 priority substances, none of which is active pharmaceutical ingredients. The Commission proposed (in 2012)[224] inclusion of three active pharmaceutical ingredients (E2, EE2 and Diclofenac) in the list of priority substances. The Commission also proposed a watch-list mechanism for gathering monitoring data to support future reviews of the list. The compromise reached during the political negotiations (Directive 2013/39/EU)[225] led to the three active pharmaceutical ingredients being placed on the first watch list, with the aim of gathering monitoring data "*for the specific purpose of facilitating the determination of appropriate measures to address the risk posed by those substances*". The first watch list will need to be established within twelve months of the entry into force of the new directive. MS will be obliged

[220] Based on information provided by SustainPharma (Sweden), RIVM (the Netherlands) and UBA (Germany), in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[221] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (WFD).
[222] Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 81/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council (EQSD).
[223] Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration (GWD).
[224] EC, Proposal for a Directive of the European Parliament and of the Council amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy, COM(2011) 876 final, available at ec.europa.eu/environment/water/water-dangersub/pdf/com_2011_876.pdf
[225] 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, OJ L 226, 24.8.2013, p.1

to monitor substances on the watch list at least annually at a limited number of representative monitoring stations for up to four years. The substances could be included in the next revision of the priority substances list.

The Marine Strategy Framework Directive (MSFD, 2008/56/EC)[226] could be relevant to medicinal products since it refers to the Water Framework Directive list of priority substances and mentions medicinal products in its Annex III, Table 2 which is an indicative list of pressures and impacts on marine regions; such pressures and impacts include contamination by hazardous substances (where the list of priority substances and medicinal products are mentioned), which are to be taken into account notably for the assessment of marine waters, the determination of good environmental status (in each marine region or subregion), the establishment of environmental targets and monitoring programmes[227]. Environmental quality standards set by the EQSD would therefore apply in the coastal area covered by MSFD.

In order to meet the objective of good water status by 2015, the Water Framework Directive also requires significant quantities of pollutant discharges in river basins to be identified and relevant quality standards to be set. The inclusion of substances that should be targeted is decided by each MS. MS could potentially include medicinal products as a specific pollutant based on Water Framework Directive Annex VIII, which provides only an indicative list of the main pollutants. In addition, if active pharmaceutical ingredients are some day included in the Water Framework Directive list of priority substances, they could be included in Annex VIII pursuant to Article 22(5) of the Water Framework Directive[228]. The objective is to consider medicinal products in the same way as other chemical substances and to be able to set up environmental quality standards, provided they represent a potential environmental risk.

Provisions relative to the chemical status in the GWD could include medicinal products if identified by MS on the basis of Water Framework Directive Annex VIII, as Article 6 of the GWD provides that MS must take measures necessary to prevent and/or limit inputs of hazardous and non-hazardous substances into groundwater, for those pollutants listed in Annex VIII of the Water Framework Directive, and any other non-hazardous pollutants not listed in the Annex but considered by MS to present an existing or potential risk of pollution.

However, it seems that MS have not generally established, through national legislation, environmental quality standards for medicinal products for the monitoring of water status[229]. In Sweden for instance, only voluntary analyses in outlet from sewage treatment plants and in recipients have been performed[199]. In the Netherlands, official maximum permissible concentrations (MPC) have been set for certain active substances but are not yet included in national legislation and, consequently, they are not monitored on a regular basis in surface water bodies. These official MPCs concern chloroquinebisphosphate, clotrimazol and miconazolnitrate;

[226] Directive 2008/56/EC of the European Parliament and of the Council of 17 June 2008 establishing a framework for community action in the field of marine environmental policy (Marine Strategy Framework Directive) (MSFD).
[227] MSFD, Annex III, Table 2 'Pressures and impacts', referred to in Articles 8 ('Assessment'), 9 ('Determination of good environmental status'), 10 ('Establishment of environmental targets') and 11 ('Monitoring Programmes'). With regards to contamination by hazardous substances, Table 2 of Annex III reads: "Introduction of synthetic compounds (e.g. priority substances under Directive 2000/60/EC which are relevant for the marine environment such as pesticides, anti-foulants, pharmaceuticals, resulting, for example, from losses from diffuse sources, pollution by ships, atmospheric deposition and biologically active substances".
[228] Article 22(5) of the WFD provides: "Where a substance on the list of priority substances adopted under Article 16 is not included in Annex VIII to this Directive or in Annex III to Directive 96/61/EC [IPPC Directive], it shall be added thereto".
[229] Based on information provided by SustainPharma (Sweden), RIVM (the Netherlands) and UBA (Germany), in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.

ad-hoc MPCs are available for estradiol and ethinylestradiol, and MPCs are currently being derived for Amidotrizoic acid, Carbamazepine, Metoprolol and Metformin[230].

Finally, it is important to note that a particular problem that arises in respect of pharmaceutical residues is the nature of their entry into surface, ground and coastal waters. That is, residues that enter waters through livestock urine and manure are diffuse pollution, which does not permit end-of-pipe treatment (Howarth, 2011). However, the Water Framework Directive and GWD both provide that inputs of pollutants from diffuse sources must be taken into account[231].

- **Monitoring and controls under the Drinking Water Directive and the Directive on natural mineral waters and spring waters**

The Drinking Water Directive (98/83/EC)[232] aims to protect human health from the adverse effects of any contamination of water intended for human consumption; drinking water must be "wholesome and clean"[233]. In order to be considered wholesome and clean, drinking water must comply with quality standards set by the Directive as regards microbiological, chemical and organoleptic parameters[234]. It does not include standards for medicinal products at EU level and the presence of pharmaceutical residues therefore does not prevent drinking water from being considered to meet an acceptable standard; the World Health Organisation has not (so far) recommended the establishment of guideline values for medicinal products in drinking water. However, MS may set values for additional parameters not included in the Drinking Water Directive if necessary to protect human health; the values set will have to ensure that the water is "*free from any micro-organisms and parasites and from any substances which, in numbers or concentrations, constitute a potential danger to human health*"[235]. MS may therefore investigate and consider establishing quality standards for medicinal products, if necessary[236].

Waters used for the abstraction of drinking water must therefore meet the requirements of the Drinking Water Directive, but also the requirements set forth in the Water Framework Directive, including the quality standards established for priority substances listed in Water Framework Directive Annex X[237]. However, Directive 2013/39/EU included three pharmaceutical substances in the watch list, but not in the list of priority substances. In addition, it results from the consultation of various national agencies that, to this day, national legislation does not usually include standards for the monitoring and control of active pharmaceutical substances in drinking water[238], although some interesting private initiatives exist. For instance, an extensive set of medicinal products is measured by RIWA (Dutch Association of River Water Supply Companies) in the Rhine and Meuse rivers; and the Dutch water companies regularly measure some of the pharmaceutical residues, but these differ depending on the company[239].

[230] Based on information provided by RIVM, in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[231] See WFD Article 10 and GWD Article 6(2).
[232] Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. It amended and replaced, with effect as of December 2003, Council Directive 80/778/EEC of 15 July 1980.
[233] Articles 1 and 4 of the Drinking Water Directive, supra.
[234] See Article 4 and Annex I of the Drinking Water Directive, supra.
[235] Article 4(1)(a), referred to in Article 5(3) of the Drinking Water Directive, supra.
[236] Interview with EUREAU
[237] WFD, Article 7 'Waters used for the abstraction of drinking water'.
[238] Based on information provided by RIVM (the Netherlands), UBA (Germany) and the French authorities, and also by SustainPharma (Sweden), in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[239] Based on information provided by RIVM in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study. See www.riwa.org

Finally, the Directive on natural mineral waters and spring waters (2003/40/EC)[240] does not appear relevant regarding contamination by medicinal products as it sets concentration limits for constituents of natural mineral waters which are present in the water naturally and do not, therefore, result from contamination at source. It's however worth noticing that a recent French study founds traces of pharmaceuticals in mineral waters[241]..

- **Monitoring and controls under the Urban Wastewater Treatment Directive (UWWTD)**

The objective of the Urban Wastewater Treatment Directive (UWWTD, 91/271/EEC) is to protect the environment from the adverse effects of urban wastewater[242] discharges and discharges from certain industrial sectors[243]. The UWWTD sets principles and obligations for the collection and treatment of urban wastewater, including as regards discharge from urban wastewater treatment plants to receiving waters, and industrial wastewater. In addition, the IED does not apply to urban wastewater treatment plants covered by the UWWTD. However, the IED does apply to independently operated treatment of wastewater (not covered by the UWWTD) and discharged by an installation covered by the IED, which includes activities of production of pharmaceutical products[244]. The environmental quality standards established under the Water Framework Directive list of priority substances apply to such installations[245]. However, the manufacturing of pharmaceutical products or the carrying out of medical activities (hospitals in particular) do not appear in the industrial sectors subject to the Directive, listed in Annex III, and there are no provisions that require the monitoring or control of residues of medicinal products.

Discharges from hospitals, which are the source of significant quantities of medicinal products in their wastewater (anaesthetics, anti-cancer, etc.), are treated in wastewater treatment plants. There is currently no legal obligation for the pre-treatment or special treatment of such discharges. Even if such treatment was carried out, the measures may not eliminate antibiotics and other medicinal products, resulting in their subsequent entry into the aquatic ecosystem (Pauwels, 2006), especially during pandemic conditions (Ellis, 2011). However, in the case of hospitals, analyses of their sewage water have generally displayed levels of pharmaceutical residues similar to those from households as (i) the ratio professionals/patient is generally 5-10 to 1 (excretion being mainly from hospital professionals) and (ii) there is a higher dilution factor in hospital sewage water as hospitals consume and expel larger volumes of water than households[246].

[240] Commission Directive 2003/40/EC of 16 May 2003 establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters.

[241] Summary of the study available here : www.science-et-vie.com/2013/03/30/pesticides-et-medicaments-bouteilles-eau-minerale/

[242] Urban wastewater is defined by the UWWTD as "domestic wastewater or the mixture of domestic wastewater with industrial wastewater and/or run-off rain water" (Article 2(1)).

[243] Article 1 of the Council Directive 91/271/EEC of 21 May 1991 concerning urban wastewater treatment.

[244] See IED, Annex I, 5.3 (a), 5.3 (b) and 6.11

[245] See WFD, Articles 10(2) and 10(3), and UWWTD, Annex IB(4).

[246] Answer to a questionnaire, provided by Åke Wennmalm, from SustainPharma (answer received on 2 January and 15 February 2013), in the context of the stakeholders' consultation carried out by BIOIS for the present study. This interview provided information that would be hardly accessible otherwise.

National legislation[247] does not necessarily address the issue of medicinal residues in urban wastewater, or pre-treatment of hospital sewage water. However, there are some pilot projects addressing this issue, such as Pharmafilter in the Netherlands[248]. In the UK, discharges from hospitals containing non-domestic wastewater constitute "trade effluent" and are regulated by the Sewerage Undertakers; a "trade effluent consent" may be required from the relevant Sewerage Undertaker and allows it to set conditions and limits for the discharges of hospital non-domestic waste. National guidance was adopted for healthcare wastewater discharges (WATER UK, 2011).

8.3.6 Disposal under the Waste Framework Directive

The Waste Framework Directive (2008/98/EC)[249] aims to protect the environment and human health by laying down measures for waste prevention and management. Waste management must notably be carried out without risk to water, air, soil, plants or animals[250]. The Directive also established a waste hierarchy to be applied as a priority, namely: (a) prevention, (b) preparing for re-use, (c) recycling, (d) other recovery (e.g. energy recovery), and (e) disposal.

Commission Decision 2000/532/EC[251] established a European List of Waste (LoW), which is a reference nomenclature and includes hazardous waste. The LoW is binding as to determination of the waste to be considered as hazardous waste[252]. This nomenclature refers to "wastes from the MFSU (manufacture, formulation, supply and use) of medicinal products" (07 05) but does not include in this section any active pharmaceutical ingredients as hazardous waste. However, some active pharmaceutical ingredients could potentially classified under "solid wastes containing dangerous substances" (07 05 13*). In addition, cytotoxic and cytostatic medicinal products (anti-cancer medicinal products) are classified as hazardous waste in the nomenclature, in the sections regarding "wastes from human or animal health care and/or related research" (18 01 08 and 18 02 07) and "municipal wastes and similar commercial, industrial and institutional wastes including separately collected fractions" (20 01 31).

However, pursuant to Article 7(a) of the Waste Framework Directive, a MS may consider waste as hazardous waste even though it does not appear in the list of the above-mentioned Commission Decision, if it displays one or more of the properties listed in Annex III[253]. Some medicinal products could thus qualify as hazardous waste, and therefore be classified as such under national legislation, based notably on the hazardous property H14 "Ecotoxic" referred to in

[247] Based on information provided by SustainPharma (Sweden), RIVM (the Netherlands) and UBA (Germany), in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.
[248] Based on information provided by RIVM in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study. See also www.pharmafilter.nl
[249] Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives (namely old directives on hazardous waste and waste oils: Directives 75/439/EEC, 91/689/EEC and 2006/12/EC, with effect from 12 December 2010 – see Article 41).
[250] Article 13 of the Waste Framework Directive (2008/98/EC).
[251] Commission Decision 2000/532/EC of 3 May 2000 replacing Decision 94/3/EC establishing a list of wastes pursuant to Article 1(a) of Council Directive 75/442/EEC on waste and Council Decision 94/904/EC establishing a list of hazardous waste pursuant to Article 1(4) of Council Directive 91/689/EEC on hazardous waste.
252 See Article 7(1) of the Waste Framework Directive 2008/98/EC.
[253] 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)).

Annex III[254]. The LoW and Annex III are currently being reviewed by the Commission[255]. However, it seems that some MS tend to classify as hazardous waste only cytotoxic and cytostatic medicines as required under EU legislation and, therefore, have not included other medicinal products in this category[247].This could potentially be considered as resulting from wrong interpretation and implementation of the Waste Framework Directive, notably in the light of the above-mentioned waste code 07 05 13*.

Classification of some medicinal products as hazardous waste would trigger specific obligations under the Waste Framework Directive (which already apply to cytotoxic and cytostatic medicines), notably[256]:

- Mixing of hazardous waste (with other categories of hazardous waste or with other waste, substances or materials) is banned (subject however to certain possible derogations); and
- In the course of collection, transport and temporary storage, hazardous waste must be packaged and labelled in accordance with applicable international and Community standards.

The above provisions on hazardous waste do not however apply to hazardous waste produced by households[257].

The provisions regarding the end-of-life of non-use medicinal products in Directives 2001/83/EC (medicinal products for human use) and 2001/82/EC (veterinary medicinal products) are quite succinct but nonetheless provide that:

- MS must ensure that appropriate collection systems are in place for medicinal products that are unused or have expired[258]; and
- The packaging of medicinal products must indicate the specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place[259].

The Waste Framework Directive also includes a brief reference to waste collection schemes for medicinal products, for which no registration is necessary[260] (see section 7.3.1).

[254] Annex III, H14 of the Waste Framework Directive (2008/98/EC) currently specifies that ecotoxic waste is "waste which presents or may present immediate or delayed risks for one or more sectors of the environment".
[255] More information on ec.europa.eu/environment/waste/framework/list.htm and ec.europa.eu/environment/waste/framework/pdf/Technical_proposal_tc.pdf (technical proposal)
[256] See Articles 17 through 19 of the Waste Framework Directive (2008/98/EC).
[257] Article 20 of the Waste Framework Directive (2008/98/EC).
[258] Article 127b of Directive 2001/83/EC (medicinal products for human use), supra; and Article 95a of Directive 2001/82/EC (veterinary medicinal products), supra.
[259] Article 54(j) of Directive 2001/83/EC (medicinal products for human use), supra; and Article 58(j) of Directive 2001/82/EC (veterinary medicinal products).
[260] § 17 of the whereas of the Waste Framework Directive provides: "Waste collection schemes which are not conducted on a professional basis should not be subject to registration as they present a lower risk and contribute to the separate collection of waste. Examples of such schemes are waste medicines collected by pharmacies, take-back schemes in shops for consumer goods and community schemes in schools".

8.3.7 Food legislation

EU food legislation is also relevant to the issue of hazards related to medicinal products, in particular concerning human health.

Veterinary medicinal products must be monitored in live animals and animal products for human consumption. Indeed, Council Directive 96/23/EC[261] extended the monitoring of a certain number of residues of pharmacological substances, as monitoring applied at the time only to farm animals and fresh meat obtained from these animals[262]. This Directive lays down measures to monitor substances and groups of residues listed in its Annex I, which includes veterinary medicinal products. Monitoring must be carried out by the operators themselves (self-monitoring) and through inspections by national competent authorities (official control measures). Residues or substance groups referred to in Annex I to the Directive must be detected by type of animal, their feeding stuffs, including drinking water, and primary animal products[263].

Regulation (EC) 470/2009[264], which repealed and replaced Council Regulation (EEC) 2377/90[265], laid down Community procedures for the establishment of residue limits of pharmacologically active substances in food stuffs of animal origin, which was later complemented by Commission Regulation (EU) 37/2010[266] setting these maximum residue limits.

A number of other EU pieces of legislation may apply to the question of residues of medicinal products in foodstuffs, such as legislation on agricultural products[267] or feed additives[268]. In the case of feed additives, Regulation (EC) 1831/2003 on additives for use in animal nutrition expressly provides that it does not apply to veterinary medicinal products as defined in Directive 2001/82/EC (previously and extensively referred to), with the exception of coccidiostats and histomonostats used as feed additives.

Although the question of food safety and more particularly of pharmacologically active substances in foodstuffs of animal origin has long been addressed by EU legislation, it nevertheless focuses on veterinary medicinal products; i.e. medicinal products that are directly administered to animals, and therefore result in direct transfer to the humans consuming them. However, the legislation does not address the potential issue of bioaccumulation, where there

[261] Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products and repealing Directives 85/358/EEC and 86/469/EEC and Decisions 89/187/EEC and 91/664/EEC.
[262] Council Directive 86/469/EEC of 16 September 1986 concerning the examination of animals and fresh meat for the presence of residues.
[263] See Annex II to Council Directive 96/23/EC, supra.
[264] Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council.
[265] Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.
[266] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.
[267] See notably Council Regulation (EEC) No 2092/91 of 24 June 1991 on organic production of agricultural products and indications referring thereto on agricultural products and foodstuffs.
[268] See Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition; Commission Regulation (EC) No 429/2008 on detailed rules for the implementation of Regulation (EC) 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives.

could be an indirect transfer to humans of substances used in medicinal products for human use because of the contact of food animals with a pharmacologically polluted environment (to feed, drink, etc.) (see section 6.1.4). Active pharmaceutical ingredients used both in veterinary medicinal products for food producing animals and medicinal products for human use are nonetheless de facto subject to the minimum residue limits set for residues of veterinary medicinal products.

8.3.8 Lack of EU soil legislation

The issue of soil pollution in general may be addressed indirectly in various EU policies, such as water (e.g. soil pollution leading to pollution of groundwater), waste, chemicals, etc. However, there is still no specific soil legislation at Community level, despite the Commission's efforts in favour of the adoption of a Soil Framework Directive.

In 2006, the Commission published its Thematic Strategy for Soil Protection, which consists of a Communication of the Commission (COM(2006) 231) (COM, 2006a), together with a proposal for a framework directive (COM(2006) 232) (COM, 2006b).

The overall objective of the Thematic Strategy is protection and sustainable use of soil (COM, 2006a). The Commission considers that action is required at local, national and European level, adding that action at Community level will have an added value by contributing to the protection of the health of European citizens that can be impaired in different ways by soil degradation, for instance because of exposure to soil contaminants by direct ingestion (children in playgrounds) or indirect intake (through contaminated food or drinking water) (COM, 2006a). This position would also apply to soil contamination by medicinal products, whether for human or veterinary use.

The proposed Soil Framework Directive constitutes the first pillar of the Thematic Strategy, and has as its principal aim the protection and sustainable use of soil. The proposal is a framework Directive, which entails that MS will be required to take specific measures to address soil threats. The proposal requires MS to identify risk areas where soil degradation processes occur (COM, 2006b). The action proposed includes measures to limit the introduction of dangerous substances into the soil, to avoid accumulation in soil that would hamper soil functions and create a risk to human health and the environment (COM, 2006b). The contaminated sites identified by MS would then have to be remediated.

In November 2007, the European Parliament adopted its first reading of the proposed Soil Framework Directive by a majority of about two thirds. However, since then no progress has been made in the adoption of the proposal, as, at the March 2010 Environment Council, a minority of MS blocked further progress on grounds of subsidiarity, excessive cost and administrative burden, as reported in a policy report on the implementation of the Strategy (COM(2012) 46) published by the European Commission in February 2012 (EC, 2012).

To this day, there is therefore a gap in EU environmental legislation as soil contamination (by pharmaceutical residues or other), and its potential consequences and impacts on human health, is not addressed. Although MS have adopted national legislation on soil, this legislation does not

usually include provisions regarding soil contamination by medicinal substances[269]. The potential issue of bioaccumulation of such substances (see section 6.1.3) is therefore not taken into account.

8.4 Section summary

8.4.1 Good Manufacturing Practices (GMP)

- GMP-related documents do not take into account the risks that medicinal products may pose to the environment at the manufacturing stage; and
- Certain MS, and in particular Sweden, are asking for a modification of GMP to include emissions to the environment resulting from the manufacturing of medicinal products, without any tangible results thus far.

8.4.2 REACH

- Medicinal products are for the most part exempted from REACH requirements, so as to avoid double regulation;
- Medicinal products are however not exempted from the REACH provisions applying to restrictions on the manufacturing, placing on the market and use of certain dangerous substances and preparations. However, Annex XVII to REACH does not currently impose restrictions regarding active pharmaceutical ingredients. There are derogations for medicinal products from certain restrictions applicable to the use and placing on the market of carcinogenic, mutagenic and reprotoxic (CMR) substances as substances or in mixtures for supply to the general public; but restrictions could target certain active pharmaceutical ingredients, but also the manufacturing process itself; and
- A potential gap therefore lies in the fact that the EU legislation on medicinal products does not cover all lifecycle stages of the products (in particular manufacturing and formulation), but at the same time medicinal products are exempted from many Titles under REACH.

8.4.3 Monitoring and controls under the Industrial Emissions Directive (IED)

- The IED applies to the production of pharmaceutical products, including intermediates. It may however not be a sufficient tool to cover emissions from

[269] Based on information provided by SustainPharma (Sweden), RIVM (the Netherlands) and UBA (Germany), in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.

the manufacturing of medicinal products as certain special provisions would not apply to small and medium companies, because of the application of consumption thresholds). The IED also applies to the intensive rearing of poultry and pigs;

- The IED does not yet include any active pharmaceutical ingredients in the list of polluting substances in the air and water, and therefore does not set emission limit values for such APIs or require their monitoring. However, active pharmaceutical ingredients could fall within groups 4 and 5 of water pollutants listed in Annex II;
- Best Available Techniques Reference Documents (BREFs) do not recommend any associated emission levels concerning active pharmaceutical ingredients. Installations but nevertheless respect BAT as they also include the way in which the installations is designed, built, maintained, operated and decommissioned; and
- If medicinal products were to be included in the list of priority substances established under the Water Framework Directive, their emissions would have to be monitored and controlled. It would then be possible to obtain data on medicinal product emissions from the European Pollutant Release and Transfer Register (E-PRTR), and the emissions would be subject to limit values.

8.4.4 Monitoring and controls in agriculture and farming under the Sewage Sludge Directive

- The Sewage Sludge Directive focuses mainly on limit values for heavy metals in soil, but does not refer to residues of medicinal products;
- There is no obligation to monitor or regulate medicinal products residues present in sewage sludge; and
- The use of sewage sludge in agriculture is sometimes restricted within MS (e.g. in Bavaria and Nordrhein-Westphalia) to take into account of the environmental risks posed by the presence of pharmaceutical residues.

8.4.5 Water legislation

Water Framework Directive and daughter Directives

- The Water Framework Directive does not specifically target medicinal products any more than any other group of substances. The Commission proposed (in 2012) the inclusion of three active pharmaceutical ingredients (E2, EE2 and Diclofenac) in the list of priority substances. The Commission also proposed a watch-list mechanism for gathering monitoring data to support future reviews of the list. The compromise reached during the political negotiations (see Directive 2013/39/EU) led to the three active pharmaceutical ingredients being placed on

the first watch list. MS will be obliged to monitor substances on the watch list at least annually at a limited number of representative monitoring stations for up to four years; the substances could be included in the next revision of the priority substances list;

- The Marine Strategy Framework Directive (MSFD) could be relevant as it also refers to the Water Framework Directive list of priority substances and mentions medicinal products in the context of pressures and impacts (which include contamination by hazardous substances) on marine regions. Such pressures and impacts are to be taken into account notably for the assessment of marine waters, the determination of good environmental status (in each marine region or subregion), the establishment of environmental targets and monitoring programmes. Environmental quality standards set under the Water Framework Directive would therefore apply in the coastal area covered by MSFD;
- MS could identify medicinal products as specific pollutants pursuant to provisions of the Water Framework Directive (Annex VIII), which could then lead to the application of quality standards and measures in surface and/or groundwaters, but most MS have not done so; and
- Pharmaceutical residues entering waters come from diffuse and point sources. The Water Framework Directive and its daughter directives include provisions regarding both types of pollution, but point sources are generally easier to identify and address.

Monitoring and controls under the Drinking Water Directive and the Directive on natural mineral waters and spring waters

- The EU Drinking Water Directive does not include quality standards for medicinal products, and the presence of pharmaceutical residues therefore does not prevent drinking water from being considered to meet an acceptable standard; the World Health Organisation has not (so far) recommended the establishment of guideline values for medicinal products in drinking water; and
- The Directive on natural mineral waters and spring waters sets concentration limits for constituents of natural mineral waters that are present in the water naturally and do not, therefore, result from contamination at source However a single recent study in France found human medicinal products in bottled mineral water[270].

Monitoring and controls under the Urban Wastewater Treatment Directive (UWWTD)

- The manufacturing of medicinal products and the carrying out of medical activities (e.g. in hospitals) are not subject to the UWWTD;
- There are no provisions under the UWWTD that require the monitoring or control of residues of medicinal products (e.g. from sewage treatment plants);

[270] Available at : www.science-et-vie.com/2013/03/30/pesticides-et-medicaments-bouteilles-eau-minerale/

- EU legislation does not impose that wastewater from hospitals be pre-treated; and
- National legislation does not necessarily address the issue of medicinal residues in urban wastewater, or pre-treatment of hospital sewage water, but in certain countries (e.g. the UK), conditions and limits may be imposed for the discharge of healthcare wastewater.

8.4.6 Disposal under the Waste Framework Directive

- The EU List of Waste mentions pharmaceutical wastes, but the only medicinal products explicitly mentioned as hazardous waste are cytotoxic and cytostatic pharmaceuticals, although some could potentially be classified under "solid wastes containing dangerous substances" (07 05 13*). However, application of the hazardous properties to assess pharmaceutical substances should result in the classification of a number of pharmaceutical wastes as hazardous wastes (notably because of their ecotoxicity (H14)); and
- Although national legislation could classify other medicinal products as hazardous waste, MS have generally not done so.

8.4.7 Food legislation

- EU food legislation requires the monitoring of veterinary medicinal products in foodstuffs of animal origin, but does not refer to medicinal products for human use; and
- Therefore, EU food legislation does not address the issue of indirect transfer to humans of residues of medicinal products for human use, which may be present and have accumulated in the natural environment of food animals. Active pharmaceutical ingredients used in both veterinary medicinal products for food producing animals and medicinal products for human use are nonetheless de facto subject to the minimum residue limits set for residues of veterinary medicinal products.

8.4.8 Lack of EU soil legislation

- There is no EU soil legislation: the proposal for a Soil Framework Directive presented by the Commission in 2006 has yet to be adopted;
- EU legislation does not address the issue of soil contamination by medicinal products, although such contamination could have impacts with regards to food safety (bioaccumulation issues); and
- The national soil legislation of MS does not usually include provisions on soil contamination by pharmacologically active substances.

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Chapter 9: Possible solutions

The objective of the present chapter is to identify possible solutions aimed at effectively reducing the release of medicinal products into the environment, increasing the current knowledge on the issue and/or fostering the elimination or removal of medicinal products.

An extended list of possible options is presented here. However, no impact assessment of these options is made, as this is beyond the scope of this study. The effectiveness of the proposed solutions to cope with the environmental impact of medicinal products would need to be further assessed, in light of their impacts on the use of medicinal products and the protection of public health. A table included at the end of each section identifies options which are considered to be the most promising and those whose implementation is suggested as a priority. However, it would be premature to recommend any specific option at this stage.

9.1 Non-legislative solutions

This section presents a number of non-legislative actions aimed to effectively reduce the release of medicinal products into the environment and/or foster their elimination or removal. As mentioned in the introduction to this chapter, these actions were identified based on the outcomes of the present study and a review of the literature. They pertain to various means (academic, technical, economic, behavioural, governance-related means, etc.) and call upon each stakeholder's active involvement (patients, doctors/veterinarians, pharmacists, pharmaceutical companies, health insurance companies, local authorities, environmental and medicine agencies, etc.).

These actions may be grouped into the following nine strategic areas:

- Developing the concept of green pharmacy and adapting packaging to influence consumption;
- Developing and harmonising the implementation of collection schemes for unused medicinal products;
- Developing source separation measures and wastewater treatments;
- Actively involving public society and professionals through information and education;
- Prioritising and monitoring molecules and/or environmental compartments of concern;
- Consolidating existing knowledge, ensuring transparency and facilitating access to information;
- Improving governance and building up an eco-pharmacovigilance network;
- Implementing incentive economic instruments; and
- Developing the knowledge base through fostering of research activities.

These actions were prioritised based on an internal brainstorming as well as stakeholders' inputs throughout the study. The most promising actions concerning the challenges raised by medicinal products, as well as suggested actions for primary intention, are highlighted in section 9.1.10. This prioritisation is however preliminary and would need further investigation before recommending certain options specifically.

9.1.1 Developing the concept of green medicinal products and adapting packaging size to influence consumption

An approach to minimising the persistence, bioaccumulation and impacts of medicinal products on the environment would be to promote the replacement of substances of concerns by molecules with a more environmentally-friendly profile[271] or substances which demonstrated a higher rate of removal in waste water treatment plants[272] and to develop new compounds that are altogether effective, efficient and readily biodegradable in the environment. It is often argued that developing greener medicinal products raises great technical and economic challenges, especially in the context of the increased externalisation of research and the increased pressure to find new candidates (Snape, 2012) (see section 7.1). The modification of active substance structures that already are known to be efficient for health purposes may sometimes be a potential vehicle of progress towards greener medicinal products that utilises already existing candidates. Glufosfamide is such an example[273]. Developing greener medicinal products is a promising strategy in the long-run (Action 1).

An additional mitigation practice would be to promote good environmental practices to help minimise releases from manufacturing sites.

Within the pharmaceutical industry, some companies focus on developing greener technologies and processes for the production of medicinal products (Action 2). The biopharmaceutical company Astrazeneca[274] developed several initiatives accordingly: e.g. Acid/Base, Alkylating Agent and Amide Formation Reagent Selection Guides, which provide environmental information to promote careful consideration of environmental impact when reagents are chosen; Substance Avoidance Database, which lists all substances on relevant regulatory lists

[271] In this context, the environmental classification system developed in Stockholm is an example of best practice allowing the promotion of more environmentally-friendly alternatives to substances of concerns.

[272] For example, the Impact Assessment to the proposal for revised WFD and EQSD directives and the inclusion of medicinal products on the priority list of substances (6019/12 ADD 2; dated 2 February 2012) pinpointed a Roig's study (2010) which shows that several Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) exist that could be used instead of Diclofenac, with similar therapeutic efficacy but allowing better removal in Urban waste water treatment plants. Likewise, replacing EE2-based oral contraceptives with progestongens-based pills could be advantageous in terms of rate of removal in urban waste water treatment plants.

[273] A new product was scheduled for animal and human drug trials which is similar to an older version of a birth control pill from the drugmaker Schering–Plough (Lubick, 2008). The new-old drug uses natural estrogens paired with a biodegradable progesterone. Further information at: www.thresholdpharm.com/sec/glufosfamide

[274] www.astrazeneca.com/Home

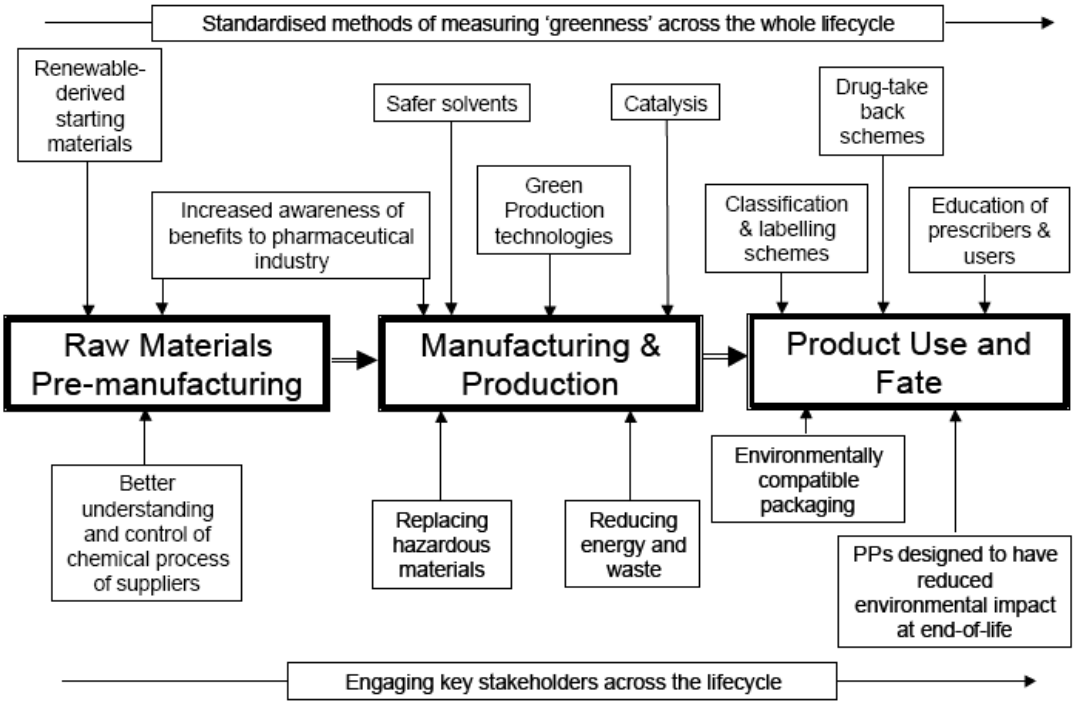
from around the world to highlight substances that should be avoided when developing manufacturing processes)[275]. These efforts from the industry could be better recognised through the inclusion of environmental criteria in GMP guidelines (See section 9.2.2.1).

It would also be good for the pharmaceutical sector to reconsider the way some medicinal products are delivered (e.g. standard packaging) to better match users' needs and to prevent the generation of unused medicines (Besse, 2010b) (Action 3). This however may question the whole organisation of pharmaceutical distribution in some MS and may call for a careful investigation of economic and safety implications before implementation. An alternative could be that the marketing authorisation holder grants a marketing authorisation for pharmaceutical forms and packaging which fits the patients's needs if this is not already the case, i.e. have the appropriate size to comply with the posology. This would help avoid unnecessary consumption, help avert extensive costs for the healthcare system and prevent generation of unused medicines. However, this option will create costs for marketing authorisation holders who may need to change the packaging lines and vary marketing authorisation dossiers.

Another aspect that could be questioned to reduce the consumption rate is whether expiration dating markedly underestimates the actual shelf life of drug products. Based on testing and stability assessment in the U.S., it was found that 88% of the lots were extended at least 1 year beyond their original expiration date, but the additional stability period was highly variable (Lyon et al. 2006). Specific data could then be collected to check if this is also true in the EU and if drug products, when properly stored, can be extended past the currently established expiration date without risk for consumers.

Figure 14 summarises "green" approaches and opportunities identified which could be applied to reduce the impact of PPs on the environment at all stages in the lifecycle.

[275] Further information on the environmental responsibility highlighted by Astrazaneca: www.astrazeneca.com/Responsibility/The-environment/Product-environmental-improvement



Source: (KNAPPE, 2008)

Figure 13: Ecopharmaco-stewardship approaches & opportunities to develop new generation of green and sustainable pharmaceutical products

Table 4: Actions focused on the production and packaging of medicinal products

Action 1	Fostering research activities for the development of green medicinal products	Pharmaceutical companies Research laboratories	R&D
Action 2	Further developing green technologies and application of green processes in manufacturing	Pharmaceutical companies	Manufacturing
Action 3	Reconsidering the adequacy of packaging sizes to consumers' needs	Pharmaceutical companies	Manufacturing and marketing

9.1.2 Developing and harmonising the implementation of collection schemes for unused medicinal products

Take-back schemes for unused medicinal products represent one of the simplest ways, with great potential, to reduce inputs of pharmaceutical products into the environment.

Regarding human medicines, whatever the type of organisation in charge of collection schemes (e.g. government-owned companies, environmental non-profit organisations, pharmaceutical federations, etc.), pharmacists and other retailers are the key actors in collection of unused medicines due to their privileged relationships with patients (see Box 7). Their systematic involvement would benefit the collection of unused medicines (CYCLAMED, 2011). Yet, the collection of unused medicines may only represent a supplementary constraint for them so far (CYCLAMED, 2011). In order to increase the implementation and efficiency of collection schemes for human medicinal products, pharmacists' responsibilities could be clarified and better used within collection initiatives (Action 4). Some MS, like France[276] and Norway, have even made their contribution mandatory.

Furthermore, better communication, within pharmacies and/or retailing points, could further help increase awareness of such schemes (see section 9.1.4). Providing streamlined information to patients regarding the importance and current efficiency of the collection of unused medicines could increase their awareness and modify practices accordingly (Action 5).

Box 7: Examples of collection schemes relying on pharmacies' involvement

Created in 1993, Cyclamed[277] is a non-governmental organisation financed by pharmaceutical companies. Through incineration of unused pharmaceutical medicines, it aims to collect and eliminate pharmaceutical residues brought back to pharmacies by consumers and/or health care centres. In 2011, 14555 tons of unused medicines were collected, with an efficiency of about 55 % given the estimated stock (CYCLAMED,

[276] French law 2007-248, art.32, Official Journal of 27/2/2007 and decree n°2009-718, Official Journal of 19/6/2009
[277] www.cyclamed.org/

2011).

SIGRE[278] in Spain was founded in 2003 by the pharmaceutical industry and is now operational in 20000 pharmacies in Spain.

Valormed[279] was agreed on by the Ministries of the Environment and the Economy in Portugal in 2001 for the management of the Integrated Management of Packaging Waste Medicines. Medicines are collected by more than 2800 pharmacies. In 2010, they collected 838 tonnes of packaging waste and discarded medicines, which represents an increase of 17% over the previous year[280].

In the veterinary sector, some countries attempted to organise the collection of unused medicines. In France, for instance, veterinaries contributed to developing a specific legislative framework[281] in this respect. Breeders that would like their medicines to be collected must bring them to the veterinaries. In 2007 in Portugal, the organisation in charge of the collection of unused human medicinal products, Valormed, extended the scope of its action to veterinary medicinal products.

The feasibility of and potential benefits from better structuring of the collection of unused medicinal products, as is being done in most MS for human medicinal products, could be systematically assessed (Action 6). Should these results be conclusive, appropriate systems to collect veterinary medicines could be elaborated and implemented in close relation with the agricultural professions and veterinarians (Action 7).

In any case, the effectiveness and adequacy of existing disposal schemes for unused medicines could be reviewed to highlight inefficiencies and best practices. In this context, a European guideline that harmonises the rules of collection (Roig, 2010b), identifies key technical and economic leverages as well as actors, and shares best practices could be developed (Action 8).

[278] www.sigre.es/index_eng.aspx
[279] www.valormed.pt
[280] www.valormed.pt/index.php?option=com_content&view=article&id=26&Itemid=84
[281] www.veterinaire.fr/documents-v2/onv_documentsP.htm

Table 5: Actions focused on the collection of unused medicines

Action 4	Better valorise the role of pharmacists in the collection of unused medicinal products	Pharmacists Organisations in charge of the collection system National authorities	Waste management
Action 5	Provide streamlined information to patients regarding the importance and current efficiency of the collection of unused medicines		
Action 6	Assessing the benefits of structuring the collection of unused veterinary medicinal products	National authorities	Waste management
Action 7	If relevant, developing adequate collection schemes in close collaboration with agricultural professions and veterinaries	Agricultural professions Veterinaries Pharmaceutical companies National authorities	Waste management
Action 8	Developing and publishing European guidelines for the successful implementation of collection schemes	National authorities Medicine agencies Organisations in charge of the collection system	Waste management

9.1.3 Developing source separation measures and wastewater treatments

Source separation measures are strategies that aim to avoid releasing high loads of medicinal products and/or hazardous substances into the municipal sewage networks, by ensuring the sorting of hazardous waste in hospitals and/or performing *in situ* treatments of effluents from manufacturing plants, hospitals and/or livestock farms. In this respect, the environmental and economic relevance of promoting separate treatment of hospital effluent is still debated. Some argue that this approach is not suitable because of the small contribution of hospitals to the overall environmental load (less than 10% of urban effluents) (Kümmerer, 2009). In this respect, Igos et al. (2012) showed centralised waste water treatment plants upgraded with advanced treatments were more efficient from an environmental perspective than decentralised treatments (e.g. treatment of hospital releases). On the other hand, others point out the potential cost-effectiveness of such measures that would contribute to reducing the need for and cost of end-of-pipe treatments, in particular in light of the significant releases by somes sources of specific hazardous molecules, which concentrations in the environment may not be acceptable. For hospital-specific substances such as cytostatics, endocrine therapy or contrast media, it is indeed shown that hospitals may be major contributors to the overall environmental load (eg. 70-90% in Denmark). In Denmark, in the Capital Region, substantial and targeted efforts were made to find out how large hospital contributions are compared to contributions from diffuse sources, and pinpoint the possible need for source separation. As a result, a demonstration project is being conducted at Herlev Hospital (in 2013-2015) with a full scale

treatment plant, where the goal is to show that cleaning of hospital wastewater can be a win-win situation which saves money (by savings on discharge taxes via direct discharge to the local water area) and protects the environment from hazardous substances[282]. The implementation of source separation must therefore be efficient for specific molecules and local contexts. Thus, before developing and investing in such separation systems, better knowledge of the origin, nature (toxicity, mutagenicity) and amount of releases from the different sources (Besse, 2010b) is required (Action 9).

Before thinking of implementing advanced wastewater treatments which can present technical and economic challenges, the removal of pharmaceuticals can be increased in conventional treatment plants by changing the treatment terms (e.g. increasing the number of times effluent is passed through the system, increasing the time spent within the system).

The design and implementation of advanced waste water treatments are time-consuming and require long-term investments. In this respect, Abegglen et al. (2009) provide some cost estimates to upgrade urban waste water treatment plants to remove oestradiol.For Switzerland, an increase of 5 to 25% in relation to conventional treatment costs depending upon the size of the treatment plant was estimated, resulting overall in 11 to 18euros per inhabitants per year depending on the number of plants to be upgraded. As explained in the Impact Assessment to the proposal for revised WFD and EQSD directives (6019/12 ADD 2; dated 2 February 2012), these costs would fall on water companies and likely passed to consumers, at least partly, via their water bills.

However, advanced wastewater treatments are however considered key strategies in the load of pharmaceutical residues in the environment (see Box 8). UV technologies show a comparatively reduced environmental performance when matched to other advanced post-treatments (Igos et al., 2012). Although recent improvements in treatments technologies make it possible to achieve substantial rates of elimination/removal for some medicinal products by destroying unavoidable remnants of active substances and metabolites (e.g. using activated carbon, advanced oxidation (ozonation) (Joss, 2008) or UV (Putschew, 2007)), this approach may not be sustainable from an energy consumption perspective and/or a cost-effectiveness standpoint (Høibye, 2008). Furthermore, many utilities may not have the necessary personnel expertise to incorporate efficiency into solicitations for design services, or to evaluate project proposals on an energy performance basis (Jones, 2007).

In order to be effective, treatments must however be supplemented by the regular maintenance of sewerage networks to prevent releases through leakages. They also must be complemented by the improvement of treatment capacity of sewage treatment plants to prevent overflows due to extreme events (AQUAREF, 2009), especially in the context of changing climate (Action 10). In comparison, WHO did not consider advanced drinking water treatment to be necessary, unless elevated levels of medicinal products are measured. WHO came to this conclusion because of the generally very low concentrations of medicinal products in drinking water and the absence so far of demonstrated risks to human health (WHO, 2011) at the current levels (despite the lack of knowledge about the impacts of long-term exposure). It is also less costly for society and more

[282] Comment from a representative from Denmark, provided in the context of the study.

pertinent from an environmental perspective to aim to reduce the pharmaceutical load before the discharge of residues into the natural environment[283].

Box 8: Advanced sewage treatment methods (Ledin, 2012)

Physical methods

Among promising physical methods are different kinds of filters (sand filters, disc filters, membrane, micro and ultra-filters), which can be used to remove particle-bound medicinal products. Membranes with very small pore sizes such as those used for reverse osmosis, nanofiltration and ultrafiltration can be used for direct removal of some medicinal products. Several types of sorbents (activated carbon, minerals and molecular imprinted polymers) have characteristics that justify evaluating their ability to remove medicinal products.

Chemical methods

Among promising chemical methods are advanced oxidation processes (e.g. Vacuum-UV, UV/H_2O_2, H_2O_2/O_3 and UV/O_3) and selective oxidation reagents (ClO_2, MnO_4- and O_3) that can be used to oxidise medicinal products. Through these treatments, medicinal products generally lose their potency and become more easily biodegradable. Selective reagents can be used for removing a very broad spectrum of medicinal products, and advanced oxidation processes might be the appropriate solution for cases in which a complete oxidation of organic material is necessary to destroy medicinal products that are difficult to remove with other methods. In particular, ozonation results in the elimination of over 80 % medicinal products, with an observed reduction of ecotoxic effects while also remaining economically reasonable and feasible in specific cases as well as manageable for wastewater treatment plant personnel.

Biological methods

Improved biological methods can be applied to biological degradation of a broad spectrum of medicinal products. Traditional biological wastewater treatment has been used to partly remove or degrade some medicinal products, and degradation may be enhanced by increasing the sludge age in existing biological treatment or by cleaning the effluent in new processes developed for that purpose. A more radical option is to use membrane bioreactors for removal of the medicinal products by extended biodegradation.

Advanced wastewater treatments cannot, as a stand-alone option, sufficiently reduce emissions into the environment (AQUAREF, 2009). Preventive actions, such as changes in behaviour of manufacturers and consumers associated with increased awareness, could be prioritised over end-of-pipe actions. Advanced wastewater treatment can be considered as a key contributor to controlling the environmental load of medicinal products where that load cannot be sufficiently controlled by source-control means (Action 11), but it requires appropriate planning and capital investment which makes it only applicable in the medium term. The need for such treatment, and the operating costs where such treatment technology has been installed, could be limited/reduced by transition to more sustainable production, consumption and disposal patterns.

Table 6: Actions focused on wastewater management

Action 9	Assessing the relevance of source separation measures and applying these measures where relevant	Health care infrastructures / Livestock farmers Local authorities	All

[283] Based on information provided by UBA (Germany) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study

Action 10	Ensuring appropriate maintenance and design of sewage networks and wastewater treatment plants	Wastewater handling and treatment services Local authorities	All
Action 11	Developing advanced wastewater treatments.	Wastewater handling and treatment services Local authorities	All

9.1.4 Actively involving public society and professionals through information and education

Raising public and health professions' awareness of the potential impacts of medicinal products in the environment could foster responsible prescription/purchase of medicines, use and disposal. Communication/education can target several categories of stakeholders, comprising EU and government authorities, pharmaceutical producers, those responsible for prescribing medication and other healthcare professionals, pharmacological committees, patients and environmental and water agencies (Wennmalm, 2010). Combinations of tailored and broad information as well as various communication channels are required to efficiently reach the audiences targeted.

The development of a benchmark of best practices at the EU level and in relevant third countries, considering various stages of the life cycle of medicines, typologies of actions and categories of stakeholders, would allow for an assessment of the relevance, feasibility, efficiency and transferability of such practices (Action 12). This compilation could then be shared e.g. in the form of leaflets amongst relevant stakeholders (e.g. Best practices for pharmacies; Best practices for consumers; Best practices for farmers) and/or be used by policy-makers to facilitate specific actions. Consequently, this could foster the EU-wide application of best pilot and/or isolated initiatives, based on resulting lessons.

Experience demonstrates that properly informing doctors, pharmacists and patients contributes to the modification of practices contributing to the input of APIs into the aquatic environment. Because these three categories of stakeholders are responsible for the prescription, delivery and/or administration/consumption of medicines, they are priority targets for education/communication programs to foster changes in behaviour.

In order to better inform patients or animals' owners, close relationships with doctors/veterinarians and/or pharmacists can be established as communication channels which can in turn be made more effective by raising awareness within these professions. Studies indeed show that patient satisfaction in primary care settings depends more on effective communication than on receiving an antibiotic prescription (Butler, 1998) (Kallestrup, 2011) (Macfarlane, 1997). Rutten et al. (1991) observe: "Professional medical advice impacts patients' perceptions and attitude towards their illness and perceived need for antibiotics, 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". The aim is that patients use medicines only when necessary and, if possible, following a prescription to increase compliance with their treatment.

For this purpose, there is a need to increase the consideration of environmental aspects in pharmacology, in particular during medical education and advanced training, e.g. by policy makers in education and health care (Besse, 2010b) (Action 13). In France, raising awareness among hospital personnel was highlighted in a 2009 Convention signed between the Health Ministry and Unions representing hospitals[284] in the "Grenelle" context[285]. At the MS level, some organisations routinely organise communication actions to train healthcare professionals, such as CESPharm[286] for pharmacists. To be successful, such a measure requires acquiring robust knowledge of potential environmental hazards and effects of medicinal products for the environment in the relevant MS.

Information could also be widely communicated through the development and publication of an environmental classification of medicinal products (Roig, 2010b), such as that developed in Sweden and recommended in the KNAPPE report (KNAPPE, 2008) (See Box 9). A framework for such a classification could ideally be developed at the European level to ensure the consistency of the approach, while taking into account MS specificities during its implementation (Action 14). Although the experience in Sweden did not fully achieve expected results in terms of modifications of prescriptions, mostly because of the lack of alternative and "greener" medicines, it must have increased the overall awareness of the profession[287].

Box 9: Swedish environmental classification of medicinal products

Communication with producers has yielded a joint project in Sweden between healthcare stakeholders and pharmaceutical producers resulting in a system for classification of environmental risk and hazard of human medicines. The system is operated by the producers under surveillance of an independent party and has produced risk and hazard classification of about 420 pharmaceutical substances so far (amounting to about 70 % of the pharmaceutical sales in Sweden). Medicinal products are classified following Persistence, Bioaccumulation and Toxicity criteria (ranging from 0 to 3), synthesised in a PBT index (from 0 to 9) with a degree of uncertainty. The higher is the index of the substance, the greater is the danger for the environment. This is associated with the assessment of their toxic risk for the aquatic environment (insignificant if PEC/PNEC<0.1; low if 0.1<PEC/PNEC<1; moderate if 1<PEC/PNEC<10 and high if PEC/PNEC>10). This classification is presented openly (www.fass.se) and in three different levels (directed to patients, prescribers, and experts like pharmacological committees). Swedish County Council produces an annual printed version of the classification to enhance use of the data for prescribers, other health care professionals, patients and water authorities. A web-based version is also available (www.janusinfo.se) (Wennmalm, 2010).

Displaying environmental information in leaflets[288] or labelling on the packaging could also contribute to making public society an actor with respect to its own consumption (Action 15). In particular, medicinal products could be (more noticeably) labelled with "return unused medication to a pharmacy" to encourage more responsible disposal (Roig, 2010b). The legislation on medicinal products foresees that the outer packaging or, where there is no outer packaging, the immediate packaging, highlights specific precautions relating to the disposal of unused

[284] Convention portant engagements mutuels dans le cadre du Grenelle de l'Environnement avec les fédérations hospitalières. Available at : www.sante.gouv.fr/IMG/pdf/convention-2.pdf
[285] www.legrenelle-environnement.fr/-Version-anglaise-.html?rubrique33
[286] www.cespharm.fr/fr/Prevention-sante
[287] Based on a communication from Ake Wennmalm, in the context of the experts'consultation carried out by BIO for the present study.
[288] E.G. Requirements for disposal can be included in the SmPC and in the patient leaflet (Based on the questionnaire filled by FAMPH in the context of the stakeholders' consultation carried out by BIO for the present study)

medicinal products or waste derived from medicinal products, where appropriate, in addition to making reference to any appropriate collection system in place. In order to be effective, this measure could, however, be in coherence with the collection system in place. More generally, the effectiveness of such measures could be further assessed. As for developing a specific label highlighting "greener" pharmaceuticals, as suggested in the literature, this option seems challenging, especially since there is still no clear definition and/or criteria of what a "green pharmaceutical" actually is.

More generally, organising sustained information campaigns, using media such as TV, Internet and radio, allows for the targeting of a large audience, amongst public society and health and environmental professions. Successful examples in France include communication campaigns about Cyclamed in 2011, which provided information about antibiotic consumption or more generally about use of medicines[289]. Following the TV communication campaign organised by Cyclamed in July 2010, a 26% increase in volumes collected in August 2010 compared to August 2009 was observed (CYCLAMED, 2011). Similarly, in Sweden, an increase in collection of about 12% occurred between 2006 and 2007 attributed to the intensive public awareness campaign carried out at the end of 2006 by Apoteket AB (Gagnon, 2009). Because of the substantial costs and resources involved, these communication campaigns should be developed after carefully identifying needs for communication and specific targets. The results, including the audience targeted and reached, as well as uptake of key messages of the campaigns, could be followed up to assess their efficiency and to build on them in subsequent communication actions (Action 16).

Last but not least, communication to national and local authorities, as well as environmental and medicine agencies, through tailored policy briefs highlighting current issues and best practices, could be put forward to gather their support in financing, designing and/or implementing e.g. recommendations from the present report (Action 17).

Table 7: Actions focused on information and education

Action 12	Developing a benchmark of best practices at the EU level and in relevant third countries	Authorities Environmental and water agencies Medicine agencies NGOs Consumer organisations	All
Action 13	Integrating environmental considerations into medical education and advanced training	Policy makers Environmental agencies National authorities	Prescriptions Delivery Use
Action 14	Developing European guidelines for the implementation of harmonised approaches for the environmental classification of medicinal products in MS	National authorities Medicine agencies Environmental and water agencies	Prescriptions Marketing Use
Action 15	Including (more noticeably) environmental aspects in the product leaflet and/or labelling	National authorities Pharmaceutical companies Medicine agencies	Marketing Use Waste

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

		Environmental agencies	management
Action 16	Organising information campaigns and assessing their efficiency	Authorities Environmental and water agencies NGOs	All
Action 17	Developing tailored policy briefs highlighting key issues and best practices	Environmental and water agencies NGOs Medicine agencies	All

9.1.5 Prioritising and monitoring active substances and/or environmental compartments of concern

Currently, results of prioritisation exercises can be very different depending on the objectives of the exercise (e.g. health and/or environmental protection (AQUAREF, 2009)) and the approach considered (hazard-based vs. risk-based) (See section 7.5.1). These exercises would benefit from coordination efforts at the regional level in order to establish lists of substances for routine monitoring regarding health and environmental purposes, and this could take into account the local and regional exposure situation as well as available analytical methods. This involvement of the private sector in the design and harmonisation of monitoring campaigns would better guarantee the relevance of the selection of medicinal products and metabolites to be monitored - either routinely or in an ad-hoc manner (based on the production and consumption peak, etc.) (Actions 18 & 19).

Despite the recent technical and methodological improvements, academics, pharmaceutical companies and authorities could work together on developing standard methods (including for example standardised sampling and analysis protocols) and improving detection/analytical tools, in water, but in particular in soils, sludge, sediments and biota (Action 21). In France, in 2008, AQUAREF[290] prepared an inventory of research laboratories working in the field of monitoring of medicinal products in the various environmental compartments along with methods used for different types of active substances. This initiative could be generalised in other MS (Action 20). Further collaboration for the design of monitoring methods between research laboratories and operational levels in charge of the monitoring would facilitate their dissemination and application in the field (AQUAREF, 2009). The increased demand for analytical services by public organisations/authorities (e.g. water agencies) in the context of national monitoring campaigns represents an interesting opportunity to develop these methods.

Results of surveys and monitoring campaigns relating to emerging pollutants are increasingly published in the EU. In the Czech Republic, Kozisek et al. reported the results of a survey of human medicinal products in drinking water from public water systems supplying 5.3 million people (i.e. 50% of the population) (Kozisek et al., 2013). A number of studies focusing on the monitoring and human health risk assessment of trace amounts of pharmaceuticals in drinking water were also conducted in the Netherlands. These include the Schriks et al. (2010)'s study on

[290] www.aquaref.fr

the Toxicological relevance of emerging contaminants of drinking water quality, and the Versteegh et al. (2007)'s study on Pharmaceuticals in drinking water and resources for drinking water[291]. In France, ANSES published in March 2011 the results of its national campaign on the occurrence of medicines in raw and treated water (ANSES, 2011). Another report is expected to be published this year by ANSES on the assessment of risks to human health from Carbamazepine and Danofloxacine[292]. Measures for researching dangerous substances in water (RSDE) in classified facilities for environmental protection (ICPE) are also ongoing in France[293]. However, no pharmaceutical substances are included in the list of substances operators in France must monitor. Nonetheless, considerations have been given to including pharmaceutical substances in this list following contamination of a river where a link has been observed between discharges from a pharmaceutical plant and impacts on the fish in the river (Action 22).

Table 8: Actions focused on prioritisation and monitoring

Action 18	Improving and harmonising monitoring and prioritisation strategies	Environmental and water agencies	All
Action 19	Involving the private sector in the design of monitoring campaigns	Pharmaceutical companies	All
Action 20	Establishing an inventory of research laboratories and methods used for the monitoring of medicinal products	Authorities Research laboratories	All
Action 21	Harmonising methods in water, soil, sludge, sediments, biota		All
Action 22	Monitoring systematically specific active substances and/or compartments of concern, based on prioritisation exercises		All

9.1.6 Consolidating existing knowledge, ensuring reporting transparency and facilitating access to information

There is a need to better structure mechanisms of information exchange, collect scattered data and harmonise reporting formats in order to improve transparency, comparability and use of information related to medicinal products at the EU level (See section 7.5.3). This concerns marketing data, end-of-life data, monitoring data as well as toxicological and eco-toxicological information. In particular, the following actions could be fostered.

There is also a need to streamline information and provide the most appropriate information to public authorities, in order to facilitate the implementation of relevant measures, particularly in

[291] available through www.rivm.nl

[292] Communication from the French Health Ministry, in an official note specific to the present study, in the context of the stakeholder's consultation conducted by BIO.

[293] Based on information provided by the French authorities in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

terms of disposal and treatment (Action 23) and ensure that summaries and key endpoints are publicly available. Controlled access to confidential data related to ecotoxicological and toxicological assessment performed in the ERA could also be granted to public authorities.

The development of an EU database gathering existing but scattered or unpublished non-confidential data generated by research or authorisation processes would also benefit the understanding of potential risks of medicinal products and strengthen the current knowledge base (Action 24). This would provide a better overview of the ecotoxicological knowledge of a range of substances and would for instance facilitate the development of greener pharmaceuticals. Swedish company AstraZeneca[294] can be cited here concerning best practices as they provide environmental risk evaluation data relating to their medicines on their website and make them publicly available via the Swedish Doctors Prescribing Guide, FASS.se website, using the voluntary disclosure system introduced by the Swedish Association of the Pharmaceutical Industry (LIF). A total of 27 substances with environmental data are included in this database. However, those ERA data most often do not correspond to EMA ERA data requirements; pharmaceutical companies might have their own calculation (often on acute data instead of long-term data) and thus end up with different results. In any case, the publication of any environmental data available in the Summaries of product characteristics could be encouraged (Action 25). This could be developed in combination with a monograph approach, as described in section 9.2.1.1.

Box 10: Examples of good practices at the EU level

In the water field, several initiatives to share and publish data on emerging pollutants have been implemented, notably following the development of the NORMAN network[295] in the context of the FP6 research program of the European Commission, which focuses on, amongst other pollutants, medicinal products and personal care products. This network involves a classification scheme allowing assessment of the quality of data reported, based on metadata information. The user can then select the most relevant data according to its quality. Another successful precedent in harmonising the data-sharing format is the implementation of WISE (the Water Information System for Europe). This contains data reported by MS on the monitoring of pollutants in the aquatic environment under EU Directives including the Water Framework Directive. WISE also includes data from monitoring conducted by the JRC in cooperation with a network of laboratories. Although it does not yet include monitoring data reported by the MS on medicinal products, this system is able to accommodate such data, and some JRC monitoring data on medicinal products are already included.

Because information on the collection of unused medicines and the efficiency of national collection schemes is often missing[296], stakeholders in charge of collection (pharmacies, wholesalers, and/or veterinaries, etc.) and coordination (e.g. Cyclamed in France, SIGRE in Spain) could systematically report the amount of unused medicines collected. This would help identify inefficiencies and tailor approaches (e.g. communication campaigns, incentives to the active involvement of pharmacists) to increase the collection rate (Action 25).

[294] www.astrazeneca.com
[295] www.norman-network.net
[296] Based on responses to questionnaires developed by BIO for the present study.

Relevant retailers and pharmacists could contribute to the development of transparent databases on internet sales and OTC sales respectively in order to better estimate the quantities of medicines sold. Bookkeeping of OTC sales is already implemented in a number of countries, such as France (KNAPPE, 2008) (Action 26). As it is not the role of retailers and pharmacies to develop and implement databases, their role would mainly consist in communicating about the quantities of medicines sold.

Lastly, national or EU central repositories for monitoring (occurrence, ecotoxicological effects, etc.), marketing and end-of-life data could be further developed following a harmonised format. Such initiatives could include the recent developments in the EU, e.g. based on the work of the PROTECT consortium[297]. Two Internet databases have been published that provide an inventory of national medicinal products consumption data and pharmaco-epidemiological studies at the EU level (see Box 11) (Action 27).

Box 11: EU Databases related to pharmacovigilance activities

The **inventory of Drug Consumption Databases** in Europe is a comprehensive and structured source of information on medicinal product consumption in Europe for human medicines. It comprises two documents. The master document contains a detailed report of the available information, methods to retrieve this information, a description of the validity of national medicinal product consumption data and a discussion. The country profile document summarises the main results by country. This is a work in progress and information last updated in October 2012 is now available for 17 EU countries (Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Norway, Poland, Portugal, Spain, Sweden, The Netherlands, and The United Kingdom).

Website address: www.imi-protect.eu/frameworkRep.shtml

A specific surveillance network with an associated database concerns the use of antimicrobials for humans: the **European Surveillance of Antimicrobial Consumption Project**

Website address:

www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/02/WC500070810.pdf

The **PROTECT ADR database** has been updated as of 30 June 2012. The database is a downloadable Excel file listing in MedDRA PT or LLT all adverse drug reactions (ADRs) listed in section 4.8 of the Summary of Product Characteristics (SPC) of medicinal products authorised in the EU according to the centralised procedure. This database is updated every 6 months.

Website address: www.imi-protect.eu/methodsRep.shtml

Specifically for veterinary medicines: the European Medicines Agency started the **ESVAC**[298] **project** in April 2010 following a request from the European Commission for the Agency to develop a harmonised approach for the collection and reporting of data on the **use of antimicrobial agents** in animals from MS.

Table 9: Actions focused on transparency and access to information

Action 23	Granting access to confidential data gained during authorisation of substances to environmental	Commission EMA MA holders	All

[297] For more information: www.imi-protect.eu/about.shtml
[298] www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

	authorities, and providing summaries and key endpoint in open access.	National authorities	
Action 24	Creating an EU database gathering existing non confidential data generated by research or authorisation processes	Commission EMA National authorities Medicine agencies	All
Action 25	Publication of any environmental data available in the Summaries of product characteristics	MA holders	Marketing
Action 26	Developing a systematic reporting of unused medicines collected	Pharmacists Organisations in charge of collection	Waste management
Action 27	Developing systematic reporting of the marketing of OTC medicinal products and internet sales	Retailers Pharmacies	Marketing
Action 28	Developing EU central repositories for monitoring, marketing, and end-of-life following a harmonised format	Commission EMA Pharmaceutical companies Retailers Pharmacies Authorities Environmental and water agencies	All

9.1.7 Improving governance and building an eco-pharmacovigilance network

Sustainable management of potential risks posed by the presence of medicinal products in the environment requires overcoming divisions and/or lack of communication between:

- the private sector and public authorities;
- the environmental and health sectors;
- academics, risk assessors and risk managers.

There is a need for stronger coordination and collaboration among stakeholders to figure out how the impact of medicinal products can be prevented or/or reduced at all stages in their lifecycle.

The recruitment of personnel with an eco-toxicology background in regulatory medicine agencies dealing with human and veterinary medicinal products could aid in further integrating environmental perspectives into the risk assessment and could foster collaboration with environmental and water agencies (Action 29).

Strengthening the interface between academics and risk assessors by fostering exchanges (e.g. through physical meetings) could help identify and overcome bottlenecks in the environmental

risk assessment to develop robust and practical assessments (data, methods, knowledge, etc.) (Action 30).

Better coordination between risk assessors and managers to ensure that risk mitigation measures required in the marketing authorisation are continuously improved, monitored and followed-up, was highlighted in the previous chapter. This could be implemented through physical meetings and/or regular reporting, highlighting areas of improvement and best practices.

Lastly, the involvement of the private sector in the design of monitoring campaigns (e.g. manufacturing companies, see Action 19 section 9.1.5) and in handling expired medication (e.g. pharmacy/wholesaler, see Action 5 section 9.1.2) would contribute to increase the relevance, coherence and efficiency of these actions.

More ambitious, and beyond these isolated actions, a dedicated network for eco-pharmacovigilance could be established at the EU level to coordinate science and activities concerning detection, assessment, understanding and prevention of adverse effects or other problems related to the presence of medicinal products in the environment which affect human and other animal species (Action 31). In Sweden for example, the Swedish government commissioned the MPA to investigate environmental effects of medicinal products, to present proposals on measures to reduce environmental effects of products (nationally as well as in the EU) and to investigate how information about content and quantities of chemicals could be improved and made more available (Velo, 2008). A limited number of key representatives of experts and stakeholders from each MS could be nominated, with their primary role being to report and share MS experiences in managing potential risks of medicinal products, e.g. through a common internet platform and/or through international conferences.

Table 10: Actions focused on governance and the development of an eco-pharmacovigilance network

Action 29	Encouraging the recruitment of personnel with an eco-toxicology background in regulatory agencies	Medicine agencies MA holders	Risk assessment
Action 30	Further coordinating the work of risk assessors and managers, e.g. through physical meetings and/or regular reporting	National/local authorities Medicine agencies MA holders/pharmaceutical companies Environmental agencies	Risk assessment and management
Action 31	Establishing an EU ecopharmacovigilance network	All	All

9.1.8 Implementing economic instruments

Economic instruments could provide efficient incentives (or disincentives) to foster the production and consumption of medicines with a better environmental profile at same efficacy. Any mechanism intended to promote medicinal products with a better environmental profile by imposing costs or constraints on hazardous products probably would lead to a reduction in

innovation given the current technical and economic challenges to develop new molecules[299]. It would be more interesting to foster innovation by procuring a marketing advantage for less hazardous therapeutic options via some additional market exclusivity, which would be much more likely to stimulate a behavioural change (Taylor, 2010).

In particular, environmental aspects could be considered in the design of reimbursement schemes, which influence the consumption of medicines, particularly through prescriptions (Action 32). However, medicines for which a greener alternative does not exist should not be excluded from these reimbursement schemes, as it would penalise patients with low incomes. This is a challenging opportunity since national authorities have to ensure that marketing practices do not contribute to the overconsumption of medicines or to environmental impact while keeping the pharmaceutical markets competitive. Its implementation would be very complex and would require better knowledge regarding the substitutability of medicines as regards environmental and health criteria, which could be acquired through the development of an environmental classification of medicinal products (see Action 14 section 9.1.4).

Increasing the patent duration for more environmentally friendly alternative medicinal products compared to hazardous products may be another option, which has been suggested by the industry. It is, however, debatable from an ethical perspective, since public access to formulations and the development of "low-cost" generics would be more limited.

Table 11: Actions focused on financial incentives

Action 32	Adaptation of reimbursement schemes to integrate environmental criteria	National authorities Medicine agencies Insurance companies	Prescriptions Marketing

9.1.9 Developing the knowledge base through fostering research activities

Research activities could help bridge data gaps regarding the occurrence of medicinal products in the environment and their environmental and health effects (Action 33). Key research needs highlighted in previous chapters include:

- understanding how medicinal products get into the natural environment
- understanding the fate and behaviour of medicinal products in the environment, including a better focus on metabolites and transformation products, better knowledge of contamination of sewage sludge and of how organisms uptake medicinal products from the environment (e.g. bioaccumulation in food chain and ultimately presence in meat, fish, milk and vegetables);

[299] Cause: Regulatory requirements are increasing the duration and cost of development whilst pharmaceutical pricing is under pressure from health providers and governments. In response the industry is trying to reduce development times (to extend available patent life) and to increase the success rate in development.

- assessing chronic and ecological effects of medicinal products;
- assessing the effects of mixtures; and
- assessing risks related to antibiotic resistance.

Corresponding research activities include:

- further investigating the fate of pharmaceutical products in sewage treatment plants as well as sludge and slurry, in particular to distinguish between degradation, transformation, and elimination/removal of medicinal products (EEA, 2010);
- further developing the modelling of the transfer of pharmaceutical residues between environmental compartments, through experiments on pilot sites in catchment areas of concern (PNRM France, 2011);
- increasing knowledge on the environmental effects of pharmaceutical products, including: ecological relevance of sub-lethal responses, particularly the relevance of non-standard endpoints, the significance of antimicrobial resistance, the significance of the effects of metabolites and transformation products (KNAPPE, 2008), as well as health effects on vulnerable human groups;
- developing intelligent testing strategies for chronic toxicity assessment (e.g. based on mode of action) and aiming for the generation, documentation and public dissemination of high-quality data (KNAPPE, 2008)[300]. The generation of data on acute effects of medicinal products might be of only limited relevance for understanding the potential environmental impacts of medicinal products in the environment;
- further developing read-across, modelling and extrapolation approaches to overcome ecotoxicological and toxicological data gaps as well as lack of information on fate and behaviour of substances. They must acknowledge the sometimes drastically different life cycles, physiology and genetic make-up of environmental organisms, in comparison to standard laboratory test species;
- further investigating how mixture effects could be assessed, and identifying priority mixtures;
- implementing the research initiatives launched in November 2012 by the EU action plan against the rising threats from AMR based on 12 key actions;
- investigating potential risks associated with medicinal products in the future when considering possible climate change impacts and pandemics;
- improving knowledge about the socio-economic drivers of practices and usages of medicinal products : collective vs. individual behaviours, governance, etc. (PNRM France, 2011);

[300] Suggested by EFPIA following the Workshop on the presence of medicinal products in the environment, organised by BIO Intelligence Service on behalf of EAHC, on September 19, 2012

- collect specific data to check if the use of drug products, when properly stored, can be extended past the currently established expiration date without risk for consumers, thus justifuing a change of the information provided on packaging;
- assessing risk acceptance from social and economic perspectives (PNRM France, 2011);
- organising collaborative research within the EU on the issues of pharmaceutical residues in the environment (this may consist in organising international reviews on key issues related to medicinal products, such as Medicinal products and Personal Care Products in the Environment: What Are the Big Questions?) (Boxall, 2012); and
- mapping EU research projects and results related to environmental and health risks of the presence of medicinal products in soils and water[301].

Great research efforts have been made lately, as illustrated by a number of research projects at the European level (see Box 12).

Box 12: Examples of research projects launched at the EU scale on the issues related to medicinal products

- REMPHARMAWATER studied the fate, persistence and ecotoxicity of medicinal products in various sewage treatment plants and its effluents. Website: cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=4938731 www.unina.it/~rmarotta.
- POSEIDON evaluated technologies for the removal of medicinal products and personal care products in sewage and drinking water facilities. Website: www.eu-poseidon.com
- ERAVMIS focused on assessing the environmental impact of veterinary medicines released through the spreading of manure, slurry and sludge on agricultural land. Website: www.cranfield.ac.uk/ecochemistry/eravmis
- ERAPharm worked on improving methods and strategies for the environmental risk assessment of medicinal products. While different medicinal products were investigated, special attention was directed to three case study compounds: two human medicinal products (the Beta-blocker atenolol and the anti-depressant Fluoxetine) and one veterinary pharmaceutical (parasiticide Ivermectin)
- CYTOTHREAT is addressing the need to assess the risks of medicinal products released into the environment. The occurrence, distribution and fate of selected widely used cytostatics in different aquatic matrices, their acute and chronic toxicity and impact on the stability of the genetic material in a variety of aquatic organisms are being addressed in providing data sets necessary for scientifically based risk assessment. Special emphasis is being put on the combined effects of environmentally relevant mixtures. Website: www.cytothreat.eu

[301] EU Extrapolation from a proposal from the PNRM France (PNRM France, 2011)

- KNAPPE aimed to bundle and extend research on the occurrence of PPs in the aquatic environment as well as on the environmental and health impacts related to PPs. On this basis, the project aimed to identify the relevant priority actions to be taken in the framework of sustainable development, in terms of lowering the presence, impacts and risk of PPs. Website: www.ecologic.eu/2293
- PHARMAS is focused on two classes of human medicinal products, namely antibiotics and anti-cancer medicinal products, and it aims to obtain accurate data on both exposure concentrations and effects levels in order to conduct sound risk assessments. A prototype web-based classification system will be developed during the project with the intention of enabling all EU citizens to make their own informed decisions about the risk posed by human medicinal products to their health and to the health of the environment. The results will enable EU regulators and policy makers to make better-informed decisions on the issue of medicinal products in the environment. Website: www.pharmas-eu.org
- Innovative Medicines Initiative (IMI) is a Public-Private Partnerships between EC and EFPIA that aims to promote projects addressing bottlenecks in current medicinal product development processes. Website: www.euresearch.ch/index.php?id=745

Table 12: Actions focused on research activities

Action 33	Fostering research activities in the field of medicinal products	Researchers Policy makers	All

9.1.10 Summary of non-legislative actions and prioritisation

The actions described above were prioritised based on an internal brainstorm, as well as on stakeholders' inputs throughout the study (Table 13). The most important actions with regards to the challenges raised by medicinal products, as well as most feasible actions, are highlighted in section 9.1.10. This is a very preliminary assessment resulting from a first screening of the options. A more detailed assessment of individual and combined actions would be required as a next step to better understand associated benefits and shortcomings, from a social, environmental and economic perspective.

Table 13: Summary and prioritisation of non-legislative actions

Action 1	Fostering research activities for the development of green medicinal products	Pharmaceutical companies Research laboratories	R&D
Action 2	Further developing green technologies and application of green processes in manufacturing	Pharmaceutical companies	Manufacturing
Action 3	Reconsidering the adequacy of packaging sizes to consumers' needs	Pharmaceutical companies	Manufacturing and marketing
Action 4	Better valorise the role of pharmacists in the collection of unused medicinal products	Pharmacists Organisations in charge of the collection system	Waste management
Action 5	Provide streamline information on the importance of collecting unused medicines and the current efficiency	Pharmacists Organisations in charge of the collection system	Waste management
Action 6	Assessing the benefits of structuring the collection of unused veterinary medicinal products	National authorities	Waste management
Action 7	If relevant, developing adequate collection schemes in close collaboration with agricultural professions and veterinaries	Agricultural professions Veterinaries Pharmaceutical companies	Waste management
Action 8	Developing and publishing European guidelines for the successful implementation of collection schemes	National authorities Medicine agencies Organisations in charge of the collection system	Waste management
Action 9	Assessing the relevance of source separation measures and applying these measures where relevant	Health care infrastructures / Farmers Local authorities	All
Action 10	Ensuring appropriate maintenance and design of sewage networks and wastewater treatment plants	Wastewater handling and treatment services Local authorities	All
Action 11	Developing advanced wastewater treatments as short-term corrective actions	Wastewater handling and treatment services Local authorities	All
Action 12	Developing a benchmark of best practices in terms of training and awareness raising at the EU level and in relevant third countries	Authorities Environmental and water agencies	All

		Medicine agencies NGOs Consumer organisations	
Action 13	Integrating environmental considerations into medical education and advanced training	Policy makers Environmental agencies National authorities	Prescriptions Delivery Use
Action 14	Developing European guidelines for the implementation of harmonised approaches for the environmental classification of medicinal products in MS	National authorities Medicine agencies Environmental and water agencies	Prescriptions Marketing Use
Action 15	Including environmental aspects in the products leaflets and/or labelling	National authorities Pharmaceutical companies Medicine agencies Environmental agencies	Marketing Use Waste management
Action 16	Organising information campaigns and assessing their effectiveness	Authorities Environmental and water agencies NGOs	All
Action 17	Developing tailored policy briefs highlighting key issues and best practices	Environmental and water agencies NGOs Medicine agencies	All
Action 18	Improving and harmonising monitoring and prioritisation strategies	Environmental and water agencies Pharmaceutical companies Authorities Research laboratories	All
Action 19	Involving the private sector in the design of monitoring campaigns		All
Action 20	Establishing an inventory of research laboratories and methods used for the monitoring of medicinal products		All
Action 21	Harmonising methods in water, soil, sludge, sediments, biota		All
Action 22	Monitoring systematically active substances and/or compartments of concern		All
Action 23	Improving the communication of information that could be relevant to environmental authorities, including granting access	Commission	All

	to confidential data gained during authorisation of substances, and providing summaries and key endpoints in open access.	EMA MA holders National authorities	
Action 24	Creating an EU database gathering existing non confidential data generated by research or authorisation processes	Commission EMA National authorities Medicine agencies	All
Action 25	Publication of any environmental data available in the Summaries of product characteristics	MA holders	Marketing
Action 26	Developing a systematic reporting of unused medicines collected	Pharmacists Organisations in charge of collection	Waste management
Action 27	Developing a systematic reporting on marketing of OTC medicinal products and internet sales	Retailers Pharmacies	Marketing
Action 28	Developing EU central repositories for monitoring, marketing, and end-of-life following an harmonised format	Commission EMA Pharmaceutical companies Retailers Pharmacies Authorities Environmental and water agencies	All
Action 29	Encouraging the recruitment of personnel with eco-toxicology background in regulatory agencies	Medicine agencies MA holders	Risk assessment
Action 30	Further coordinating the work of risk assessors and managers, e.g. through physical meetings and/or regular reporting	National/local authorities Medicine agencies MA holders/pharmaceutical companies Environmental agencies	Risk assessment and management
Action 31	Establishing a EU ecopharmacovigilance network	All	All
Action 32	Adaptation of reimbursement schemes to integrate environmental criteria	National authorities Medicine agencies	Prescriptions Marketing

		Insurance companies	
Action 33	Fostering research activities in the field of medicinal products, in order to: • understand how medicinal products get into the natural environment • understand the fate and behaviour of medicinal products in the environment • assess chronic and ecological effects of medicinal products • assess the effects of mixtures • assess risks related to antibioresistance	Researchers Policy makers	All

Legend*

Most promising actions
Actions suggested for primary intention (most feasible)
Most promising actions also suggested for primary intention

*= please note that this is a very preliminary assessment resulting from a first screening of the options. A more detailed assessment of individual and combined actions would be required as a next step to better understand the advantages, shortcomings and thus the feasibility of these actions

9.2 Legislative solutions

For the sake of clarity and consistency, the structure of this section will follow that of Chapter 8: in that it will consider legislative solutions relating to:

- EU legislation regarding the marketing authorisation of medicinal products, in particular Directive 2001/83/EC on medicinal products for human use, and Directive 2001/82/EC on medicinal products for veterinary use;
- Other relevant EU legislation: however, subsections will differ from the structure of Section 8.2, as possible solutions will be presented in relation to specific steps of medicinal products' life cycle.

It must nevertheless be noted that not all identified, influential legislative factors necessarily call for legislative solutions. In some cases, non-legislative actions could be considered more adequate, necessary, or even an indispensable step before envisioning a legislative response. Other solutions may be of a transversal nature, and thus detailed in relevant sections. When this is the case, specific reference will be made to the relevant sections of section 9.2.

9.2.1 EU legislation regarding marketing authorisation of medicinal products for human and veterinary use

Identified solutions listed in the present section are to be viewed as possible amendments to EU legislation regarding the marketing authorisation of veterinary and human medicinal products (in particular Directives 2001/82/EC and 2001/83/EC, respectively), and related documents such as ERA guidelines. If an identified change would be more appropriate at the national level, clear indications are made.

Identified actions apply both to human and veterinary medicinal products, unless indicated otherwise.

9.2.1.1 Marketing authorisation (MA) process

- **MA to be substance-based, with the creation of a monograph system**

The MA, and consequently the ERA, is based on and required for the medicinal product, not the active substance, resulting in the issues identified in Section 8.1.

A possible solution could therefore be to amend the EU legislation on medicinal products for both human and veterinary use, which will ensure that the MA regarding environmental safety is based on the active substance and not on the medicinal product. This could lead to the creation of a monograph system for active substances, which would therefore contain information on the fate and effects of these substances in the environment.

This system would allow for the harmonisation of reference data, which could then be used to assess the environmental risks of all products containing the same active substance (although for

each medicinal product, specific data would be required to also assess the environmental risks posed by hazardous excipients). This would have to be updated regularly. Although this "single compound" approach would not solve the issue of the assessment of ecological effects of mixtures, it may later allow for extrapolations and therefore can be considered a preliminary step to the modelling of these effects.

In the case of an innovative product, the information contained in the monograph system, in particular ecotoxicological data, could be used for future medicinal products which would contain the same active substance, but would also be useful for different but similar active pharmaceutical ingredients.

If the monograph system option is retained, it would then be necessary to adopt a detailed approach, notably as to how the ERA of the whole medicinal product would be carried out.

The following arguments could be raised to challenge this approach:

- the relevant cost of ecological studies[302] and, consequently,
- the need for appropriate data protection to allow return on investment[303], in order to allow the pharmaceutical industry to continue the costly development of medicinal products and to maintain existing approvals and availability of medicinal products[304].

However, these two arguments do not apply for generics since for generic compounds a monograph system would reduce the costs of ecological studies (which will no longer have to be performed several times for each individual company), and it will also reduce the amount of test animals needed, in line with the EC position. In addition, the costs of ecological studies are generally low compared to the costs of toxicological studies required under the MA procedure, and the impact on the overall costs would thus be limited.

The financial burden of implementing ecotoxicological studies could be lessened through a pooling of pharmaceutical companies' resources, which could then be used to perform tests on active substances contained in medicinal products for which they apply and subsequently hold an MA. The monograph approach could benefit from the experience developed within other chemical frameworks such as biocides[305], plant protection products[306] and REACH[307].

The issue of data protection must also be taken into account. Indeed, the case of new products with patent/market exclusivity must be considered. For this type of product, there is only one marketing authorisation holder and, consequently, the cost would be proportionally higher for a

[302] Interview with a representative of the European Generic medicines Association (EGA), who indicated that the average costs of ecotoxicologial studies for one active substance is approximately €300,000. Also based on information provided by IFAH-Europe in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[303] Based on information provided by IFAH-Europe in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[304] This notably is the position of IFAH-Europe on veterinary medicinal products. See www.ifahsec.org/the-protection-of-registration-data-for-existing-and-new-veterinary-medicinal-products/
[305] Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the creation, market availability, use of biocidal products.
[306] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and the repeal of Council Directives 79/117/EEC and 91/414/EEC.
[307] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Rgistration, Evaluation, Authorisation and Restriction of Chemicals (REACH); the establishment of the European Chemicals Agency; the amending of Directive 1999/45/EC; and the repealing of Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94, Council Directive 76/769/EEC, and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

single company. One possibility would be to guarantee competent authorities free access to this data but to limit the availability of ERA data with a fee[308] for parties other than competent authorities.

The content of the monograph system mightnot be limited to the endpoints, study summaries and results of the ERA performed in the framework of the MA procedure. Indeed, it also could include all scientific data and publications that are freely available and not covered or limited by any commercial information confidentiality issues.

This "monograph approach" was indicated as a good solution by some national regulatory agencies in the context of the 2010 public consultation on a better regulation of veterinary medicinal products[309], although at the time, no clear overall position emerged on the establishment of such a monograph system for environmental risks: 34% of the respondents had no opinion, 18% were not in favour, 10% somewhat in favour and 18% clearly or very much in favour. This proposition was however supported by several experts in the field during the 2012 workshop on the presence of medicinal products in the environment organised by the project team and the stakeholders' consultation[310].

- **Requirement of an ERA for "old" medicinal products**

Medicinal products for human use authorised prior to 30 October 2005 were not subject to the requirement of performing an ERA. This also is the case for veterinary medicinal products that were authorised before performing an ERA became obligatory (i.e. prior to 1998 when the first ERA guideline for veterinary medicinal products came into force).

The performing of an ERA could be required for these "old" medicinal products to ensure that the fate and effects on the environment of currently and widely used medicinal products are taken into account. There are various possibilities, which may differ or evolve depending on whether the MA procedure and therefore the ERA remain focused on the medicinal product (notwithstanding various medicinal products using the same active pharmaceutical ingredient) or whether the MA procedure is modified for the existing procedure and based on the evaluation of the active substance:

- The requirement of performing an ERA could be systematically imposed at least at the time of the MA renewal of "old" medicinal products, i.e. when extending/prolonging the authorisation[311]. The ERA requirement also could apply to all generic medicines, whether for human or veterinary use, and when no ERA was performed for the reference medicinal product;

[308] Based on information provided by the French authorities in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[309] EC workshop, 2010. "Better regulation of veterinary medicinal products: how to put in place a simpler legal framework, safeguard public and animal health while increase the competitiveness of companies"
[310] Based on information provided by the French authorities, the Umweltbundesamt (UBA, German Federal Environmental Agency) and the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL Bund) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study;
[311] This view is shared by a number of experts and national regulatory agencies. See in particular Keessen A., Freriks A., van Rijswick M., 2012, The Legal Instruments for the control of emissions of medicines for human and veterinary use, Universiteit Utrecht, p.53; RIVM intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on 19 September 2012; Also based on information provided by RIVM and the French authorities in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

- Another possibility would be to establish a "catching up" procedure for all old medicinal products[312], whether for human or veterinary use, to assess their potential environmental risks. Such a 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 the active substance[313]. It might be useful to prioritise the molecules before assessment to decrease the financial burden on the industry[314]. Active substances that most likely pose environmental risks could be studied first[315]. Approaches to prioritisation that have been suggested by various sources could be taken into account[316];
- A system of co-evaluation and pooling of resources similar to REACH's system could be envisaged, which would allow for a sharing of financial costs incurred for performing ERAs among pharmaceutical companies ; the issue of confidentiality of results and other property matters could be dealt with within the consortia that would be created;
- In certain cases a river basin-based detailed environmental impact assessment (EIA taking into account real environmental conditions) could be more appropriate than EU-based or national ERA since size of river basins as recipients of discharged APIs or metabolites are different, and they may be easily located in different MS.

Environmental experts for assessment of MA application

One member of the CVMP is an environmental risk assessor. The CVMP is also assisted by a specific working party on environmental risk assessment composed of 10 experts[317]. However, the CHMP does not include any members with environmental expertise. The rules regarding the composition of the CHMP could therefore be modified to include at least one environmental risk assessor serving on the CHMP, and possibly other environmental experts, through the creation of a standing working party on environmental risk assessment for human medicinal products. The suggestion that environmental experts participate in working group meetings at the CHMP is further detailed in Section 9.1.7 hereafter. Regarding PBT assessment, a possible option could be to involve the European Chemicals Agency (ECHA)'s PBT Working Group in the ERA for the definitive assessment of PBT properties for medicinal products.

[312] This possible solution is not new and was proposed by the French CGEDD : see CGEDD, Médicament et environnement - La régulation du médicament vis-à-vis du risque environnemental, Report No. 007058-01, November 2010, p.29, available at. www.cgedd.developpement-durable.gouv.fr/IMG/pdf/007058-01_rapport_cle2ef48b.pdf.

[313] Based on information provided by UBA (Germany) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study

[314] The prioritisation of active substances to assess is supported by various stakeholders. Suggested by UBA (Germany) and the Swedish Medicinal Products Agency (MPA) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study. See also PNRM (2011), supra, p.12.

[315] RIVM intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on 19 September 2012.

[316] Based on information provided by UBA and Swedish MPA in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study: UBA mentions Kool et al. (2008), and Swedish MPA mentions Roos et al (2002): V. Roos, L. Gunnarsson, J. Fick c, D.G.J. Larsson, C. Rudén. Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection; Science of the Total Environment 421-422 (2012) 102–110

[317] See www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CVMP/people_listing_000037.jsp&mid=WC0b01ac0580028e2b

Table 14: Summary of actions related to the MA procedure

1.1	Developing a monograph system based on experience from the REACH, biocides and plant protection products legislation.
1.2	Testing the framework on pilot substances (practicality, costs, and robustness).
2.1	If the MA procedure remains product-based, requiring an ERA at the time of renewal or extension of the medicinal product or for generics when no ERA has been performed for the reference medicinal product.
2.2	Establishing a catching-up procedure to assess active substances (which would be more feasible if the MA procedure becomes active substance-based): ■ Prioritisation of substances to assess; ■ Results of assessment to feed the monograph system (e.g. short summaries of study reports and their assessments like for plant protection products).
3.1	Ensuring presence of environmental experts, particularly ecotoxicologists, at the EU level when it is not yet the case (amending the rules on the composition of the CHMP), and at the national level, for critical review and analysis of environmental data, in particular ERA. Experts of the ECHA's PBT Working Group could be involved in the ERA for the assessment of PBT properties of medicinal products.

At the national level, it could also be ensured that each MS regulatory agency include ecotoxicologists that participate in MA commissions, whether for human or veterinary medicinal products[318]. This is necessary for ensuring that MA applicants submit adequate and critical reviews of ERAs.

9.2.1.2 Environmental risk assessment (ERA)

The present section details possible actions regarding three main shortcomings identified in relation to the ERA, and it proposes: (i) revising ERA guidelines, (ii) ensuring ERA results have an impact on the MA process, and (iii) increasing availability of ERA data and results.

- **Revision of ERA guidelines**

As highlighted in section 8.1.2, ERA guidelines tend to limit the scope of medicinal products, whether for human or veterinary use. A revision of ERA guidelines could therefore be considered to ensure that all medicinal products undergo a thorough environmental risk assessment. Such

[318] (CGEDD, 2010), supra, p.31; and (PNRM, 2011), supra, p.12.

revision could be included in the existing review process of guidelines, as ERA guidelines are intended to be reviewed regularly. ERA guidelines could thus be revised so that comprehensive environmental information is required for allmedicinal products (e.g. no comprehensive environmental informationis required for medicinal products for domestic animals, such as flea collars for dogs).

Revision of ERA guidelines could also aim at improving the effective knowledge of the fate and effects of medicinal products in the environment. The scientific requirements for the ERA are discussed in section 8.1.2 and, in light of the findings contained in the referred section, the following actions could be envisaged, with the aim of revising the scientific requirements of the ERA guidelines:

- Reviewing the action limit applied and use of certain endpoints which do not always reflect medicinal products' and ecosystems' specificities;
- Reviewing certain calculation techniques provided in the ERA guidelines, such as calculation of PEC, and requiring the consideration of metabolites at an early stage (they are currently only considered in Phase II: Tier A for veterinary medicinal products and Tier B for human medicinal products)[319], etc.;
- Including a PBT assessment for all veterinary medicinal products, not just those entering Phase II, independently of whether they meet the trigger value; and
- The following points, which may require the acquisition of additional scientific knowledge, could also be discussed within the EMA before considering revising the ERA guidelines to include these elements:
- Consideration of the presence of other substances in the receiving environment with a similar mode of action (EEA, 2010)[320], i.e. so-called combination effects. Although the single compound approach to the proposed monograph system could potentially hinder the objective of identifying similar modes of actions, as it may not solve the issue of assessment of ecological effects of mixtures (whether mixtures in the medicinal product itself or because of substances present in the receiving environment), it may later allow for extrapolations.

Impacts of the ERA results in the MA process

ERA results are included in the risk/benefit analysis only in the MA procedure for veterinary medicinal products. EU legislation could therefore be amended to include the ERA outcome in the risk/benefit analysis applicable to medicinal products for human use, thus ensuring that the potential risks that a medicinal product may pose to the environment are taken into account. In this framework, accepted residue levels will depend on the therapeutic importance of the human pharmaceutical (EEA, 2010)[321]. That is, the MA could be refused for medicinal products that do not have significant therapeutical benefits and that also pose environmental risks; however, for a

[319] The Belgian Federal Agency for Medicines and Health Products (FAMHP) indicated, in a questionnaire created by BIOIS in the context of stakeholders' consultation for the present study, that they sometimes receive non-relevant data on fish/algae/daphnia in phase II Tier B because they know the product will not reach the environment and they have no means to require data on the metabolite which is excreted.
[320] (EEA, 2010), supra, p.11.
[321] (EEA, 2010), supra, p.10.

medicinal product which would have therapeutic benefits for a pathology but also would be harmful to the environment, adequate risk mitigation measures would have to be imposed (see section 8.1.3 and section below on risk mitigation measures[322]. However, the precautionary principle could be taken into account when determining what is an 'acceptable' environmental concentration, and thus the associated risk. This could be particularly relevant for the PBT assessment results.

More attention would thus be paid to ERA results by EMA (centralised procedure), but also by MS agencies responsible for authorising the marketing of human medicinal products, since this would imply that the granting of an MA under the decentralised or mutual recognition procedures could be denied by a CMS (see section 8.1.2).

In addition, in order to ensure an adequate risk/benefit analysis, the granting of an MA, whether for human or veterinary medicinal products, should be subject to the submission of a full ERA. Consequently, it could be decided to prohibit competent agencies, whether at the EU or national level, from resorting to post-authorisation commitments when the ERA is not complete. However, an alternative could be to establish a binding system for post-marketing commitments, with the non-submission of a complete ERA within the agreed timeframe being grounds for suspension of the MA until the MA holder complies with his obligations.

- **Availability of ERA data and results**
  - **Publication of ERA data and results in public assessment reports**

The EU legislation on medicinal products could impose, at a minimum, the publication of ERA results and endpoints in the public assessment report[323], notwithstanding the type of procedure followed for the MA (centralised, decentralised or mutual recognition). That is, ERA results could be included in European public assessment reports (EPAR) or public assessment reports (PAR) published by national regulatory agencies, and such publications should not be limited to a mere conclusion but should clearly present each step of the evaluation and underlying assumptions. Public assessment reports could display all studied elements, at least for MA with Phase II ERAs. If an evaluation stops at Phase I, reasons for its conclusion and relevant data should be provided. That is to say, there should be increased transparency of ERA. Publication of the ERA report itself could also be considered, but this must be discussed with pharmaceutical companies, as they are unlikely to accept this due to confidentiality issues, i.e. they will want to avoid giving a commercial advantage to competitors (although exceptions exist, such as AstraZeneca practices in Sweden, which publishes environmental assessment endpoints, even though they do not correspond exactly to endpoints that would result from the ERA, see section 9.1.6).

In order to harmonise environmental information provided in national PARs, these latter cases could be adapted from the EPAR's structure. That is, templates for PARs could be adapted to the EPAR templates to obtain the same level of environmental information whether under the centralised, decentralised or mutual recognition procedures.

[322] See notably (CGEDD, 2010), supra, p.28 et 31.
[323] Supported e.g. by Defra : see based on information provided by Defra in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

If a monograph system is adopted, ecotoxicological data obtained through the ERA procedure should be used to feed the monograph system with regard to the active substances that are assessed.

▷ **Availability of ERA data and results in a centralised Internet database**

Environmental data resulting from the performance of ERAs could be made publicly and easily accessible to ensure transparency and access to environmental information established under EU law. Information on, at minimum, the fate and effects on the environment of the active substance (as well as methods of analysis) could be available in a centralised database, such as a dedicated Internet portal. This database could stem from, and potentially constitute the monograph system detailed in previous sections. It therefore should include, at least, all collected existing environmental data that are not classified, i.e. not deemed of a confidential nature, whether generated through research or through the MA procedure (EEA, 2010)[324]. This issue is discussed further in section 9.1.6.

Table 15: Summary of actions related to ERA

4.1	Broadening the scope of medicinal products, whether for human or veterinary use, for which environmental information is required under ERA guidelines (i.e. include medicinal products currently stopping at Phase I without having to provide environmental data).
4.2	Revising the scientific requirements of ERA guidelines, including: ■ Reviewing the action limit and endpoints; ■ Reviewing certain calculation modalities (e.g. PEC); ■ Taking into account metabolites at an early stage; and ■ Including a PBT assessment for all veterinary medicinal products, not just those entering Phase II, independently of whether they meet the trigger value.
4.3	Discussing the following elements within the EMA, to assess whether ERA guidelines should take into account the current scientific knowledge: ■ Consideration of the combination effects of mixtures.
5.1	Including ERA results in the risk/benefit analysis for human medicinal products: acceptable residues could depend on the therapeutic importance of the medicinal products.
5.2	Applying the precautionary principle in the risk/benefit analysis to determine what is an «acceptable» environmental risk. This is particular relevant to the issue of PBT medicinal products. It would have to be applied by assessors on a case-by-case basis.

[324] (EEA, 2010), supra, p.10. Also based on information provided by FAMHP (Belgium) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

5.3 Imposing a binding system for post-authorisation commitments to ensure submission of complete ERAs.

5.4 Requiring medicinal agencies to communicate ERA results and data to water authorities and other interested parties.

6.1 Improving information provided in EPARs and national PARs:

- Publication of ERA results and endpoints as a minimum standard; and
- Harmonisation of EPARs and PARs through similar templates

6.2 Creating a dedicated centralised Internet database, which could stem from or constitute the monograph system.

9.2.1.3 Risk Mitigation Measures (RMM) and pharmacovigilance

When an environmental risk has been identified following performance of an ERA, RMM may be imposed. However, at present, these RMM only consist of recommendations in the product information (Summary of Product Characteristics and Product Leaflet). As such, the only binding obligation rests upon the MA holder who must include these recommendations in the product literature. In addition, the effectiveness of these RMM is not measured.

One possible solution would be to ensure that implementation of RMM becomes an obligation on third parties, particularly users and prescribers. Such an obligation could be imposed at the EU level (to ensure uniformity) or at the national level. However, effectively implementing such an obligation could be quite difficult, especially in terms of human and financial resources (to ensure that users and prescribers comply with RMM). The objective of ensuring the efficiency of RMM might be better achieved by educating users and prescribing physicians by providing them with knowledge and understanding of the environmental risks certain medicinal products may pose. This proposal is explained in section 9.1.4 on non-legislative solutions.

Essential to ensuring effectiveness and appropriateness of RMM are the monitoring data, for example data regarding water pollution obtained in the context of the Water Framework Directive[325], used for post-market evaluation of the authorisation. This could lead to possible revision of RMM or withdrawal of the MA. In this case, it could be necessary to amend the EU legislation on medicinal products so that it includes the possibility of amending or withdrawing approval of substances if environmental quality standards set for them under the Water Framework Directive are not met. Such a possibility is already provided for in the European regulations on plant protection products[326] and biocides[327]. If a monograph system were adopted, monitoring data should also be fed into it.

[325] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy

[326] See Plant Protection Products Regulation (EC) No 1107/2009, supra, Article 21.

As regards the pharmacovigilance systems imposed by EU legislation for human and veterinary medicinal products, only the latter requires environmental problems to be taken into account. This system however is not necessarily effective (see section 8.1.3). Effective implementation of the environmental pharmacovigilance could be better ensured for veterinary medicinal products. In addition, the provisions on pharmacovigilance for medicinal products for human use could be amended to ensure that environmental problems are taken into account.

Table 16: Summary of actions related to RMM and pharmacovigilance

7.1	Amending EU legislation on medicinal products so that monitoring data (particularly for water, obtained pursuant to the Water Framework Directive) could be used for post-market evaluation of authorisation, which could lead to possible revision of RMM or even MA withdrawal.
7.2	Implementation of existing RMMs have to be controlled
7.3	Ensuring that the environmental pharmacovigilance imposed for veterinary medicinal products is effective.
7.4	Amending Directive 2001/83/EC on medicinal products for human use to ensure that environmental problems are taken into account in the pharmacovigilance system.

9.2.2 Other EU legislation relevant to the issue of medicinal residues in the environment

This section will focus on other EU environmental legislation relating to life cycle stages of medicinal products that are not covered by EU legislation regarding the MA process of both human and veterinary medicinal products, namely: manufacturing, end-of-life, and monitoring of pharmaceutical residues in the environment following their disposal and/or use.

9.2.2.1 Manufacturing

- **REACH**

As highlighted under section 8.3.2, medicinal products are generally exempted from most Titles of REACH, which may be seen as a loophole since not all of their life cycle stages are covered by EU legislation on medicinal products. It therefore could be of interest to amend the REACH Regulation to limit exemptions applicable to medicinal products and to include within its scope the formulation and manufacturing of medicinal products. This would ensure that environmental risks of active pharmaceutical ingredients are assessed at all life cycle stages of medicinal

[327] See Biocidal Products Regulation (EC) No 528/2012, supra, Annex VI ('Common principles for the evaluation of dossiers for biocidal products'), points 67 and 69.

products[328]. The Commission and MS concluded in the recent REACH review[329] that no amendments are necessary for the time being (identified possible adjustments were balanced against the interest of ensuring legislative stability and predictability). However, changes could be considered in the future to ensure that the formulation and manufacturing of medicinal products fall within the scope of REACH. This would require an in-depth analysis as to how such inclusions would function under the REACH complex framework, such as e.g. requiring a registration dossier for the active substance for specific uses (included in the formulation and manufacturing processrd).

Another possibility could be to ensure that environmental aspects are taken into account in other relevant EU legislation dealing with the manufacturing of medicinal products.

- **Good Manufacturing Practices (GMP) and Industrial Emissions Directive (IED)**

  - **GMP**

The GMP legislation (Directive 2003/94/EC for human medicinal products, and Directive 91/412/EC for veterinary medicinal products) could be amended to consider environmental concerns related to active pharmaceutical ingredients. In particular, this would require ensuring that aspects of environmental protection fall within the scope of the GMP Guide, which is not currently the case (seen section 8.3.1). However, this could require submission of the matter to the World Health Organisation, where GMP guidelines are discussed.

This possible option should be viewed as alternative to tighten the rules applicable to water protection, waste disposal and emissions controls in the respective EU legislation.

An alternative proposal could be to amend the GMP legislation to introduce an environmental certification that could apply to pharmaceutical production facilities and that would consider environmental emissions of active pharmaceutical ingredients. The objective would also be to include an environmental perspective in the legislation for improved cleaning techniques at production facilities[330]. The feasibility of such a proposal would however have to be assessed first.

The introduction of an environmental certification is supported by some national competent authorities[331].

  - **IED**

As indicated in section 8.3.3, under the IED[332], emission limit values must be established, notably for polluting substances listed in the priority substances list under the Water Framework Directive[333]. Therefore for any pharmaceutical ingredients for which environmental quality

[328] This solution is supported by various national regulatory agencies, such as UBA and Romanian Agency for Medicines and Medical Devices. Based on information provided by UBA and the Romanian Agency for Medicines and Medical Devices in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[329] Commission's report, Review of REACH, 5 February 2013, Ref. COM(2013) 49 final, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2013:0049:FIN:EN:PDF
[330] See Report from Swedish Medical Products Agency (2009), supra. And Report from the Swedish Medical Products Agency (2011), Platform to enable the initiation of a revision of EU legislation on Good Manufacturing Practice, GMP, in order for legislation also to comprehend environmental considerations, p.8, available at www.lakemedelsverket.se/upload/eng-mpa-se/Swedish-platform-GMP-environmental-July-2011.pdf
[331] Such as the Swedish MPA (information provided in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study).
[332] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control).
[333] IED, Article 14 and Annex II.

standards were set under the Water Framework Directive, emission limit values would also be established. This could contribute to a greening of the manufacturing process of medicinal products and of the products themselves (see section 9.1.1 on green pharmacy). It could also be pertinent to include, pursuant to IED Article 14(1)(a), other active substances in the IED list of polluting substances.

It could also be appropriate to consider reviewing, and possibly revising, pertinent Best Available Techniques Reference Documents (BREFs), such as the BREF for Organic Fine Chemicals, to take into account environmental concerns related to the manufacturing of medicinal products (for instance through associated emission levels).

- **Incentives for the development of green pharmacy**

The issue of green manufacturing of medicinal products may be addressed in the framework of GMP Directives and the IED, as seen above. However, alongside green manufacturing is the issue of green pharmacy, i.e. devising human or veterinary medicinal products less harmful to the environment[334]. In order to foster and promote research and initiatives in this field on behalf of pharmaceutical companies, it could be relevant to consider and provide incentives to develop green medicinal products (see also 9.1.1). Such incentives could for instance take the form of an extension of data protection and/or patent duration for these medicinal products[335], such as:

- A revision of the European Patent Convention (EPC)[336]: until recently, this solution could have been viewed as undesirable since it does not provide for a unitary European patent (and is binding on more than the EU MS); however, this solution appears more feasible now that the European Parliament adopted the "EU patent package"[337], which includes Regulation (EU) No 1257/2012 on unitary patent protection (25 MS participate) that applies to patents granted under the EPC[338]; and
- An extension of the protection period applicable to clinical data, during which these data may not be used for MA of generic medicinal products for human (Directive 2001/83/EC, article 10) or veterinary use (Directive 2001/82/EC, article 13).

Incentives could also include a lowering of fees and taxes for green medicinal products[339].

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[334] Based on information provided by EFPIA in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study: EFPIA indicated that reference to 'green' medicinal products involves two concepts: (i) designing a medicine which inherently has a lower environmental impact, and (ii) improving processes to produce medicinal products in order to make the processes more environmentally friendly.

[335] (EEA, 2010), supra, p. 4 et 10. Also based on information provided by Defra in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study

[336] Convention on the Grant of European Patents of 5 October 1973. Available at http://documents.epo.org/projects/babylon/eponet.nsf/0/7bacb229e032863dc12577ec004ada98/$FILE/EPC_14th_edition.pdf

[337] It includes two EU regulations on the creation of a European unitary patent and the establishment of language regime applicable to this unitary patent, together with an international agreement setting up a Unified Patent Court. See notably http://ec.europa.eu/internal_market/indprop/patent/index_en.htm

[338] Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:361:0001:0008:EN:PDF

[339] Solution supported by various competent authorities, based on information provided by the Romanian Agency of Medicines and Medical Devices, AEMPS (Spain) and FAMHP (Belgium) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

However, some national authorities raised concerns about the feasibility of increasing duration of patents for green medicinal products, pointing out the following issues, which should be addressed before any legislative modification is initiated[340]:

- Criteria must be established to define the concept of "green pharmaceutical";
- Environmental data are currently not accessible and/or not exhaustive; and
- There are potential negative effects resulting in the disappearance of very important active pharmaceutical ingredients (e.g. anti-cancer).

It would indeed be important that these incentives do not result in green medicinal products being produced to the detriment of the medicinal effectiveness of the medicinal products developed for the targeted pathology. For some authorities, it therefore would preferable to promote innovation in developing ecotoxicological tests that are less costly and more robust rather than lowering the costs of (existing) tests[308]. The underlying rationale of green pharmacy is that both issues (environmental impacts and risks, and effectiveness) should be addressed concurrently. An easier alternative to providing incentives for green chemistry (such as those described above) would be to develop a label for "green medicinal products" which could *de facto* ensure marketing advantages for the less or non-hazardous products.

Table 17: Summary of actions related to the manufacturing of medicinal products

8.1	Amending REACH Regulation to limit exemptions applicable to medicinal products and to ensure that formulation and production of medicinal products are covered.
9.1	Ensuring that aspects of environmental protection related to active medicinal products fall within the scope of the GMP legislation.
9.2	Establishing environmental certifications for pharmaceutical manufacturing plants as called for by the previous feasibility assessment of such a solution.
10.1	Amending IED to include emissions limit values for active pharmaceutical ingredients where relevant, for instance when environmental quality standards have been set under the Water Framework Directive through its list of priority substances.
10.2	If deemed necessary after review, reviewing relevant BREFs and revising them to take into account environmental concerns related to the manufacturing of medicinal products (e.g. associated emission levels).

[340] E.g. French authorities (information in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study).

11.1 Extending data protection or patent duration for green medicinal products, through:

- Amendment to the European Patent Convention, notably with regards to the adoption of the "EU patent package"; or
- Extension of data protection under the EU medicines legislation, through extension of periods applicable to generic medicinal products for human or veterinary use.

11.2 Promoting innovation by lowering fees and taxes for green medicinal products or, alternatively, financing the development of ecotoxicological tests and data retrieval.

11.3 Establishing a specific label for green pharmacy.

9.2.2.2 Waste management

▶ Under the Waste Framework Directive

▷ Classification of pharmaceutical substances as hazardous waste

Currently, the only medicinal products explicitly classified as hazardous waste under EU law are cytotoxic and cytostatic (anti-cancer) medicinal products. Although MS have the option of classifying other medicinal products as hazardous waste, they generally have not done so. Some active pharmaceutical ingredients could also be classified as hazardous waste under entry 07 05 13* (solid wastes containing dangerous substances). The Waste Framework Directive[341] could nevertheless be revised to include additional pharmaceutical substances as hazardous waste, for example any active pharmaceutical ingredients identified as priority (hazardous) substances under the Water Framework Directive. It could be pertinent to consider including a general provision in the Waste Framework Directive and/or Decision 2000/532/EC establishing the List of Wastes, which would state that pharmaceutical substances added to the priority (hazardous) substances list would automatically classify as hazardous waste. This would be on the grounds that these substances display at least one of the hazardous properties displayed in Annex III to the Waste Framework Directive, namely its ecotoxic nature. This would ensure proper disposal of these substances and explicit labelling.

▷ Take-back schemes

Take-back schemes for unused medicinal products could be addressed under both (or either) the EU legislation on medicinal products and the Waste Framework Directive (all identified actions related to operational aspects of take-back schemes are dealt with under section 9.1.2).

It would first be necessary to ensure enforcement of the provisions of Directive 2001/83/EC (medicinal products for human use) and Directive 2001/82/EC (veterinary medicinal products)

[341] Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives.

regarding the setting up of take-back schemes for unused medicinal products. Some consider the legislation to be unclear as regards to the objectives and the implementation of take-back schemes[342]. The EU legislation on medicinal products could therefore be amended to better identify the objectives and functioning of take-back schemes.

Regarding the issue of extended producer responsibility (EPR, of which take-back schemes are a form), it could be relevant to include specific requirements regarding EPR for unused medicinal products. If this resulted in an amendment to the Waste Framework Directive, the new requirements would apply to all types of waste included in the directive's scope, not just pharmaceutical substances. This could be undesirable. If additional EPR requirements are adopted, they could be included in the relevant legislation on medicinal products so as to apply only to active pharmaceutical ingredients[343].

An alternative would be to create an EU-wide EPR system for unused medicinal products, whether for human or veterinary use, which would provide for a harmonised system.

However, this option is not supported by all stakeholders[344]. Some stakeholders consider any EU decision to create an EPR system for unused medicinal products should take into account already-existing systems in MS[340] (see section 9.1.2 for examples of national take-back schemes), which could otherwise face duplication. The additional legislative provisions could indicate that unused medicinal products should be returned to pharmacies, and that packaging should expressly indicate "return unused medication to a pharmacy" (EEA, 2010)[345], which would increase awareness among the public.

Regarding the creation of an EPR system for all medicinal products, some national regulatory agencies consider this solution to be currently unfeasible because of existing knowledge gaps regarding their environmental and human health impacts[346]. This further indicates that such a measure would not be proportionate in light of current knowledge and might have an unjustified impact on medicinal product development[347]. Knowledge should therefore be improved first (see section 9.1.6).

- **Under the Urban Wastewater Treatment Directive (UWWTD)**

The UWWTD[348] could be amended but not necessarily to impose new obligations for the treatment and elimination of medicinal residues in urban wastewater. The first objective would

[342] Intervention of the Environment Department of the Stockholm County Council during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on 19 September 2012.
[343] Based on information provided by the French authorities and the Romanian Agency on Medicines and Medical Devices in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study. The Romanian Agency on Medicines and Medical Devices agree that the issue would be better addressed under the medicines legislation (and not the Waste Framework Directive).
[344] E.g. EFPIA, which indicated: "We do not believe that application of EPR to medicinal products is appropriate. The proper disposal of unused medicines is a responsibility of the consumer based on proper education and publicity. We support the concept of national disposal schemes for the proper disposal of unused medicines - these should be appropriate to the circumstances of each MS." Information provided by EFPIA in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[345] (EEA, 2010), supra, p.10.
[346] Based on information provided by the Federal Agency for Medicines and Health Products (FAMHP) in a questionnaire elaborated by BIOIS in the context of a stakeholders' consultation for the present study.

[347] Based on information provided by FAMHP (Belgium) in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study
[348] Council Directive 91/271/EEC of 21 May 1991 concerning urban wastewater treatment

be to encourage improvement of wastewater treatment methodologies for the increased removal of medicinal products. Further research at the EU level would be required (see also section 9.1.9)[340]. The imposition of new obligations should be in relation to identified environmental risks and should be linked to ERA results.

However, more stringent provisions could be imposed in the case of "hot spots" such as hospitals. Although such provisions should not necessarily apply to all pharmaceutical substances, such measures could be imposed on specific molecules that have a particular impact on the environment (e.g. radionuclides, etc., but also substances identified for instance as priority substances under the Water Framework Directive). An alternative could be a non-legislative solution entailing working with professionals for good practices in healthcare facilities to provide guidance for the control of risks related to the elimination of medicines, including those in wastewater (see section 9.1.3)[349].

If urban wastewater treatment plants were required to take action to prevent or reduce pollution by pharmaceutical substances (e.g. any identified as priority substances under the Water Framework Directive), it would be important to assess the suitability of the possible technical options. The assessment should determine the extent to which the pharmaceutical residues can be removed, and include a cost/benefit analysis[350]. Wastewater treatment methodologies' guidelines for the removal or destruction of medicinal substances could be drafted, which would offer guidance and assistance, notably to urban wastewater treatment installations[351].

Table 18: Summary of actions related to the disposal of medicinal products

12.1	Reminding national competent authorities of the need to classify pharmaceutical wastes as hazardous waste, when appropriate, under entry 07 05 13* (solid wastes containing dangerous substances).
12.2	Amending the Waste Framework Directive to classify additional pharmaceutical substances as hazardous waste, such as active pharmaceutical ingredients if included in the Water Framework Directive priority (hazardous) substances list.
12.3	Including a general provision pursuant to which pharmaceutical substances added to the Water Framework Directive priority (hazardous) substances list would automatically classify as hazardous waste under the Waste Framework Directive and Commission Decision 2000/532/EC establishing the List of Wastes.
13.1	Ensuring enforcement of the provisions in existing EU medicines legislation regarding take-back schemes, and amending it to better identify the objectives and functioning of such schemes.

[349] See e.g. Information provided by the French authorities in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study, where they indicate that they are currently elaborating such guidance documents with healthcare professionals.
[350] Based on information provided by MHRA in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[351] Based notably on information provided by the Romanian Agency on Medicines and Medical Devices in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

13.2	Including specific requirements regarding EPR in the EU legislation on medicinal products.
13.3	Developing an EPR system for unused medicines at the EU level, taking into account existing initiatives at MS level.
14.1	Encouraging, potentially through legislation (e.g. UWWTD), the improvement of wastewater treatment methodologies to increase removal of medicinal products.
14.2	Imposing more stringent requirements for "hot spots", such as hospitals, at least for specific molecules that have a particular impact on the environment.
14.3	Including provisions for cost/benefit analysis regarding technological improvement of urban wastewater treatment methodologies, to determine the suitability of different options when environmental quality standards are set under the Water Framework Directive for substances including active pharmaceutical substances.
14.4	Drafting guidelines on wastewater treatment methodologies to provide guidance and assistance to wastewater treatment plants

9.2.2.3 Monitoring and controls of pharmaceutical residues in the environment following disposal and/or use

- **Water**
  - **Water Framework Directive and daughter Directives**

The Water Framework Directive is an important tool to address the issue of medicinal residues in the environment, in light of its binding nature for all MS and the fact that it includes identified timescales for action. This view is not held unanimously among the national regulatory authorities. Some support the idea[352], others emphasise possible side effects[353].

The Water Framework Directive could specify that ERA results play a role in the assessment of substances to be placed on the list of priority substances established pursuant to Article 16 of the Water Framework Directive and now due to be revised every six years. In particular, Article 16(2)(a) could make a direct reference to environmental risk assessments carried out under Directives 2001/82/EC (veterinary medicinal products) and 2001/83/EC (medicinal products for human use), as amended. Directive 2013/39/EU has already introduced an obligation to consider information gathered under both of these directives when selecting substances for the watch list. An additional action could be to include active pharmaceutical ingredients, as a group, in the list

[352] See e.g. UBA and BVL Bund, based on information provided in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

[353] See e.g. MHRA intervention during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on 19 September 2012: "possible side effects resulting from a strengthening of the legislation and the impacts it could have on human health, through a reduced access to some medication. In particular, including medicinal products in the list of priority substances under the WFD could have significant implications in terms of water treatment costs and in terms of the marketing of certain medicinal products for which less environmentally damaging alternatives do not always exist."

of the main pollutants provided under Water Framework Directive Annex VIII. However, not all such substances would necessarily be of concern. Furthermore, nothing currently prevents MS from identifying individual pharmaceutical substances as specific pollutants where they present a risk to the aquatic environment. Some such substances could already fall into the generic categories listed, and the list in Annex VIII is in any case only indicative.

Regarding the Groundwater Directive (GWD), as previously indicated under section 8.3.5, its Annex II Part B establishes a minimum list of pollutants and their indicators for which MS have to consider establishing threshold values in accordance with Article 3. Neither Annex II nor Annex I to the GWD establishing groundwater quality standards includes any mention of medicinal products. As both annexes were to be reviewed by the Commission by 16 January 2013 (GWD, Article 10), the Commission could suggest the inclusion of specific pharmaceutical substances in these annexes (although the specific technical report of the Common Implementation Strategy for the Water Framework Directive does not mention pharmaceutical substances when providing recommendations for the review of these annexes)[354]. It therefore could be relevant to include a provision in the GWD requiring that ERA results be taken into account for the review of Annexes I and II.

The Water Framework Directive and its daughter Directives could also include provisions requiring Member States to make publicly available and easily accessible (e.g. through a dedicated database such as the European Pollutant Release and Transfer Register) water monitoring data regarding substances listed in the priority substances list and watch list, irrespective of the pre-existence of environmental quality standards. Initiatives in some MS show that such an action is feasible[355]. Water monitoring data on pharmaceutical substances could be fed into the monograph system. This suggestion is to be linked to that below on increased coordination between water and medicinal products regulators.

Finally, the issue of pharmaceutical residues in the marine environment could be addressed through the Marine Strategy Framework Directive (MSFD), which also refers to the Water Framework Directive priority substances and requires that MS establish and implement monitoring programmes (see section 8.3.5). Provisions in the MSFD regarding medicinal residues could also be strengthened by creating synergies with the OSPAR[356] lists of substances[357], whether with the list of chemicals for priority action (which refers to the pharmaceutical substance diosgenin) or its list of substances of possible concern (which refers to various medicinal products in its sections A, B and D)[358]. Thus, assessed PBT medicinal products could be included in the OSPAR lists, and medicinal products included in the OSPAR lists could be referred to in the MSFD.

[354] Common Implementation Strategy for the WFD, Technical report on recommendations for the review of Annex I and II of the Groundwater Directive 2006/118/EC, Technical Report No. 7 2011-057, December 2011. Available at http://bookshop.europa.eu/en/technical-report-on-recommendations-for-the-review-of-annex-i-and-ii-of-the-groundwater-directive-2006-118-ec-pbKHAV12007/

[355] In France, the PNRM foresees the creation of an open database listing the assessment of exposure levels, which may induce health or environmental impacts, or available and previously collected ecotoxicological or toxicological data, indicating that the confidential nature of certain data and the existence of EU initiatives will have to be taken into account. See PNRM (2011), supra, p.10.

[356] Convention for the Protection of the marine Environment of the North-East Atlantic ('OSPAR Convention') of 22 September 1992. See www.ospar.org/content/content.asp?menu=00310108000007_000000_000000

[357] Intervention from Thomas Backhaus during the Workshop on the presence of medicinal products in the environment organised in Brussels by BIOIS on behalf of EAHC, on 19 September 2012

[358] See www.ospar.org/content/content.asp?menu=00950304450153_000000_000000

▷ Monitoring and controls under the Drinking Water Directive and the Directive on natural mineral waters and spring waters

The project team has identified the following possible actions to be undertaken:

- Encourage research to acquire further knowledge on the issue (see section 9.1.9);
- Monitoring of some pharmaceutical substances in drinking water could be imposed on the basis of substances to be included in the first watch list under the Water Framework Directive; and
- Especially with monitoring data and existing knowledge in mind, consider setting European quality standards applicable to pharmaceutical substances.

Similar to what is being recommended for the Water Framework Directive and its daughter Directives, the Drinking Water Directive[359] could be amended to include provisions on the disclosure to medicines regulators of monitoring data regarding specific pharmaceutical substances, so that they may be taken into account and used in the evaluation of MA applications (Keessen, 2012). These monitoring data could concern, as a minimum requirement, those pharmaceutical substances to be included in the first watch list under the Water Framework Directive.

Views and opinions vary among national competent authorities. Many consider that the time is not appropriate to regulate these substances under the Drinking Water Directive. Others state that the evidence from the published literature indicates that there is no risk to human health from exposure to human medicinal products via drinking water[360], and they highlight the lack of information on this subject, thus calling for further research to acquire additional knowledge[361]. For instance, the French regulatory agency for veterinary medicinal products (ANSES-ANMV) is currently conducting an investigation for health risk assessment related to the presence of Carbamazepine (human pharmaceutical) and danofloxacine (veterinary pharmaceutical) in drinking water[361].

However, other national agencies believe that the legislative framework on drinking water is not adequate to limit exposure of humans to medicinal residues, and they suggest that specific requirements be imposed, particularly environmental quality standards for, e.g. endocrine disrupting compounds[362]; others suggest that a threshold value of 0.1µg/l be included, on the basis of the precautionary principle, for pharmaceutical substances with effects similar to biocides and pesticides[363].

[359] Coucil Directive 98/83/EC on the quality of water intended for human consumption. It amended and replaced, with effect as of December 2003, Council Directive 80/778/EEC of 15 July 1980.
[360] Based on information provided by MHRA and EFPIA in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[361] E.g. position of French authorities (information provided by the French authorities in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study).
[362] Based on information provided by the Romanian Agency on Medicines and Medical Devices in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.
[363] Based on information provided by UBA and BVL Bund in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

▷ Increasing cooperation between water and medicinal products regulators

It could be necessary to include provisions in the current legislation (Water Framework Directive and EU medicines legislation) regarding the exchange of information between medicinal products regulators and water authorities (Keessen, 2012). This would contribute to achieving good chemical and ecological water status, which is the main objective of the Water Framework Directive. The following could be included in the relevant EU legislation (Keessen, 2012):

- The Water Framework Directive and its daughter Directives could require Member States to fully disclose the monitoring data of pharmaceutical substances required under EU legislation to the medicines regulatory agencies, whether at EU or national level, so they may be used by medicinal products regulators in the evaluation of MAs, and in particular in relation to ERAs;
- The medicinal products legislation (Directives 2001/82/EC and 2001/83/EC) could be amended to include provisions requiring that ERA data and results as well as any other environmental information provided in the framework of the MA application be made accessible to water authorities. The environmental information provided would facilitate the monitoring of active pharmaceutical substances in water (both surface and groundwater) and contribute to the establishment under the Water Framework Directive of adequate control measures and the assessment of substances to be placed on the list of priority substances or in Annexes I and/or II to the GWD. If the legislation on medicinal products is so amended, it would be relevant to mention this legislation (in particular the abovementioned directives) in part A of Annex VI to the Water Framework Directive to which Article 11(3)(a) refers. This would entail that programmes of measures established for each river basin district pursuant to the Water Framework Directive would have to include, as part of their "basic measures", measures required under the EU legislation on medicinal products;
- Water monitoring data could also be taken into account for possible reassessment of the MA once it has been granted. The legislation on medicinal products could therefore expressly mention that other EU legislation (in particular the Water Framework Directive and its daughter Directives, but also the Drinking Water Directive) could be taken into account in the MA procedure. This could lead, for instance, to a revision of RMM to ensure their appropriateness or, if an updated ERA shows that the resulting environmental risks are too high and may not be mitigated, to a withdrawal of the MA as suggested in section 9.2.1.3 (provided, in the case of human medicinal products, the ERA results are included in the risk/benefit analysis). The water monitoring data could be fed into the monograph system, if such a system is adopted.

The confidential nature of some of the data exchanged between medicines agencies and water authorities should not be viewed as an obstacle, as nothing would prevent the agency or authority receiving the information from ensuring it remains confidential. This already occurs in some MS, where medicines agencies communicate ERA-related confidential information to

water authorities, notably for research purposes, specifying that the information is of a confidential nature and must remain so[364].

Such exchange of information, in addition to improving the environmental assessment of medicinal products or substances, would also improve the eco-classification of medicinal products (EEA, 2010). Eco-classification of medicinal products is dealt with in section 9.1.4.

Table 19: Summary of actions related to monitoring and control

15.1	Including a direct reference in Water Framework Directive Article 16(2)(a) to ERA carried out under the EU legislation on medicinal products (Directives 2001/82/EC and 2001/83/EC).
15.2	Including active pharmaceutical ingredients, as a group, in Water Framework Directive Annex VIII indicative list of main pollutants.
15.3	Amending the GWD to ensure that ERA results for pharmaceutical substances are taken into account by the Commission when reviewing Annexes I and II (groundwater quality standards + list of pollutants and threshold values)
15.4	Strengthening MSFD provisions by creating synergies with the OSPAR list of chemicals for priority action and its list of substances of possible concern. Assessed PBT medicinal products could be included in the OSPAR lists, and medicinal products included in the OSPAR lists could be referred to in the MSFD.
16.1	Encouraging research to acquire further knowledge.
16.2	Requiring monitoring of some pharmaceutical substances in drinking water (e.g. substances on the Water Framework Directive list of priority substances or watch list).
16.3	Setting quality standards (threshold values) applicable to pharmaceutical substances identified as posing a risk to human health.
17.1	Amending the Water Framework Directive and its daughter Directives, but also possibly the Drinking Water Directive, to ensure Member States make publicly available and easily accessible (e.g. through a dedicated database) water monitoring data on pharmaceutical substances listed in the priority substances list and watch list, taking into account the confidential nature of certain data.

[364] Interview with a representative from the French veterinary medicines regulatory agency (ANSES-ANMV).

18.1	Amending the Water Framework Directive and its daughter Directives, but also the Drinking Water Directive, to require Member States to fully disclose to medicines authorities (whether at the EU or national level) monitoring data on pharmaceutical substances required under EU legislation.
18.2	Amending EU legislation on medicinal products to include provisions requiring ERA data and results to be made accessible to water authorities. Mentioning EU legislation on medicinal products (Directives 2001/82/EC and 2001/83/EC) in part A of Water Framework Directive Annex VI, to which Article 11(3)(a) refers (on basic measures in the programme of measures) – if amendment proposed in the first sentence is adopted.
18.3	Amending EU legislation on medicinal products to ensure that water-monitoring data communicated by water authorities are taken into account during the evaluation of MA applications and for post-reassessment of MA. Water monitoring data could be fed into the monograph system, if such a system is adopted.

- **Soil**
  - **Sewage sludge**

Provisions could be introduced into the Sewage Sludge Directive to require the monitoring of selected pharmaceutical substances. However, research could be given priority over legislation, as there is a lack of data regarding the presence of medicinal residues in sludge from sewage treatment plants[365].

The development of best practices[366] could be an appropriate option.

  - **Soil contamination**

There is no EU soil legislation, as a Soil Framework Directive has yet to be adopted. The current proposal for such a framework directive (drafted by the Commission in 2006) does not address the issue of soil contamination by medicinal products. If a new proposal is drafted, or the existing proposal amended (and adopted) by the European Parliament, this issue could be expressly taken into account, and measures to prevent and/or to limit the risk of soil pollution by pharmaceutical substances (especially with regards to veterinary medicinal products) could be included (Keessen, 2012).

At present, the issue of soil contamination by medicinal products may only be addressed through national legislation.

- **Food legislation**

[365] Supported by the French authorities (information in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study). The French authorities mention that there are only a few projects concerned with acquiring data on the presence of medicinal residues in sewage sludge; they cite Armistiq, Amperes)

366 Based e.g. on information provided by EFPIA in a questionnaire elaborated by BIOIS in the context of stakeholders' consultation for the present study.

The issue of food safety in relation to the presence of residues of veterinary medicinal products in foodstuffs of animal origin is broadly covered by EU food legislation. However, residues of human medicinal products found in the environment and entering the food chain have not yet been taken into account, except where the medicinal product has both human and veterinary use. There is a lack of knowledge and data on the issue of bioaccumulation of medicinal products in foodstuffs. The project team is therefore of the opinion that further research on this issue is required before any legislative action may be contemplated (see section 9.1.9).

Table 20: Summary of actions related to food legislation

19.1	Promoting/ requiring monitoring to collect data on the presence of medicinal residues in sewage sludge.
19.2	Amending the Sewage Sludge Directive to impose monitoring for selected pharmaceutical substances.
19.3	Cooperating with professionals to develop best practices guidance.
20.1	If the proposal for a Soil Framework Directive is adopted, it could be amended to address the issue of soil contamination by medicinal residues.

9.2.3 Summary of legislative actions and possible prioritisation

The table below summarises the various possible actions identified in section 9.2, and highlights the most important as well as the most feasible legislative actions, based on the consultants' findings and stakeholders' inputs throughout the study. This is a very preliminary assessment resulting from a first screening of the options. A more detailed assessment of individual and combined actions would be required as a next step to better understand the advantages, shortcomings and thus the feasibility of these actions.

1.1	Developing a monograph system based on experience from REACH, biocides and plant protection products legislation.
1.2	Testing the framework on pilot substances (practicality, costs, robustness).
2.1	If the MA procedure remains product-based, requiring an ERA at the time of renewal or extension of the medicinal product or for generics when no ERA has been performed for the reference medicinal product.
2.2	Establishing a catching-up procedure to assess active substances (which would be more feasible if the MA procedure becomes active substance-based): ■ Prioritisation of substances to assess; ■ Results of assessment to feed the monograph system (e.g. short summaries of study reports and their assessments like for plant protection products).
3.1	Ensuring presence of environmental experts, particularly ecotoxicologists, at the EU level when it is not yet the case (amending the rules on the composition of the CHMP), and at the national level, for critical review and analysis of environmental data, in particular ERA. Experts of the ECHA's PBT Working Group could be involved in the ERA for the assessment of PBT properties of medicinal products.
4.1	Broadening the scope of medicinal products, whether for human or veterinary use, for which environmental information is required under ERA guidelines (i.e. include medicinal products currently stopping at Phase I without having to provide environmental data).
4.2	Revising the scientific requirements of ERA guidelines, including: ■ Reviewing the action limit and endpoints; ■ Reviewing certain calculation modalities (e.g. PEC);

	■ Taking into account metabolites at an early stage; and ■ Including PBT assessment for all veterinary medicinal products, not just those entering Phase II, independently of whether they meet the trigger value
4.3	Discussing the following elements within the EMA, to assess whether ERA guidelines should take into account the current scientific knowledge: ■ Consideration of the combination effects of mixtures. ■
5.1	Including ERA results in the risk/benefit analysis for human medicinal products: acceptable residues could depend on the therapeutic importance of the medicinal products
5.2	Applying the precautionary principle in the risk/benefit analysis to determine what is an 'acceptable' environmental risk. This is particular relevant to the issue of PBT medicinal products. It would have to be applied by assessors on a case-by-case basis.
5.3	Imposing a binding system for post-authorisation commitments to ensure submission of complete ERAs.
5.4	Requiring medicinal agencies to communicate ERA results and data to water authorities and other interested parties.
6.1	Improving information provided in EPARs and national PARs: ■ Publication of ERA results and endpoints as a minimum standard; and ■ Harmonisation of EPARs and PARs through similar templates.
6.2	Creating a dedicated centralised Internet database, which could stem from or constitute the monograph system.

7.1	Amending EU legislation on medicinal products so that monitoring data (particularly for water, obtained pursuant to the Water Framework Directive) could be used for post-market evaluation of authorisation, which could lead to possible revision of RMM or even MA withdrawal.
7.2	Implementation of existing RMMs have to be controlled.
7.3	Ensuring that the environmental pharmacovigilance imposed for veterinary medicinal products is effective.
7.4	Amending Directive 2001/83/EC on medicinal products for human use to ensure that environmental problems are taken into account in the pharmacovigilance system
8.1	Amending REACH Regulation to limit exemptions applicable to medicinal products and to ensure that formulation and production of medicinal products are covered.
9.1	Ensuring that aspects of environmental protection related to active medicinal products fall within the scope of the GMP legislation.
9.2	Establishing environmental certifications for pharmaceutical manufacturing plants as called for by the previous feasibility assessment of such a solution.
10.1	Amending IED to include emissions limit values for active pharmaceutical substances where relevant, for instance when environmental quality standards have been set under the Water Framework Directive through its list of priority substances.
10.2	If deemed necessary after review, reviewing relevant BREFs and revising them to take into account environmental concerns related to the manufacturing of medicinal products (e.g. associated emission levels).
11.1	Extending data protection or patent duration for green medicinal products, through: ▪ Amendment to the European Patent Convention, notably with regards to the adoption of the "EU patent package"; or

	▪ Extension of data protection under the EU medicines legislation, through extension of time periods applicable to generic medicinal products for human or veterinary use.
11.2	Promoting innovation by lowering fees and taxes for green medicinal products or, alternatively, financing the development of ecotoxicological tests and data retrieval.
11.3	Establishing a specific label for green pharmacy.
12.1	Reminding national competent authorities of the need to classify pharmaceutical wastes as hazardous waste, when appropriate, under entry 07 05 13* (solid wastes containing dangerous substances).
12.2	Amending the Waste Framework Directive to classify additional pharmaceutical substances as hazardous waste, such as active pharmaceutical ingredients if included in the Water Framework Directive priority (hazardous) substances list
12.3	Including a general provision pursuant to which pharmaceutical substances added to the Water Framework Directive priority (hazardous) substances list would automatically classify as hazardous waste under the Waste Framework Directive and Commission Decision 2000/532/EC establishing the List of Wastes.
13.1	Ensuring enforcement of the provisions in existing EU legislation on medicinal products regarding take-back schemes, and amending it to better identify the objectives and functioning of such schemes.
13.2	Including specific requirements regarding EPR in the EU legislation on medicinal products.
13.3	Developing an EPR system for unused medicines at the EU level, taking into account existing initiatives at MS level.
14.1	Encouraging, potentially through legislation (e.g. UWWTD), the improvement of wastewater treatment methodologies to increase removal of medicinal products.

14.2	Imposing more stringent requirements for "hot spots", such as hospitals, at least for specific molecules that have a particular impact on the environment.
14.3	Including provisions for cost/benefit analysis regarding technological improvement for urban wastewater treatment methodologies, to determine the suitability of different options when environmental quality standards are set under the Water Framework Directive for substances including active pharmaceutical substances.
14.4	Drafting guidelines on wastewater treatment methodologies to provide guidance and assistance to wastewater treatment plants
15.1	Including a direct reference in Water Framework Directive Article 16(2)(a) to ERA carried out under the EU legislation on medicinal products (Directives 2001/82/EC and 2001/83/EC).
15.2	Including active pharmaceutical substances, as a group, in Water Framework Directive Annex VIII indicative list of main pollutants.
15.3	Amending the GWD to ensure that ERA results for pharmaceutical substances are taken into account by the Commission when reviewing Annexes I and II (groundwater quality standards + list of pollutants and threshold values).
15.4	Strengthening MSFD provisions by creating synergies with the OSPAR list of chemicals for priority action and its list of substances of possible concern. Assessed PBT medicinal products could be included in the OSPAR lists, and medicinal products included in the OPSAR lists could be referred to in the MSFD.
16.1	Encouraging research to acquire further knowledge (see key points of first six chapters for specific aspects).
16.2	Requiring monitoring of some pharmaceutical substances in drinking water (e.g. substances on the Water Framework Directive list of priority substances or watch list).
16.3	Setting quality standards (threshold values) applicable to pharmaceutical substances identified as posing a risk to human health.

17.1	Amending the Water Framework Directive and its daughter Directives, but also possibly the Drinking Water Directive, to ensure Member States make publicly available and easily accessible (e.g. through a dedicated database) water monitoring data on pharmaceutical substances listed in the priority substances list and watch list, taking into account the confidential nature of certain data.
18.1	Amending the Water Framework Directive and its daughter Directives, but also the Drinking Water Directive, to require Member States to fully disclose to medicines authorities (whether at EU or national level) monitoring data on pharmaceutical substances required under EU legislation.
18.2	Amending EU legislation on medicinal products to include provisions requiring ERA data and results to be made accessible to water authorities. Mentioning EU legislation on medicinal products (Directives 2001/82/EC and 2001/83/EC) in part A of Water Framework Directive Annex VI, to which Article 11(3)(a) refers (on basic measures in the programme of measures) – if amendment proposed in the first sentence is adopted.
18.3	Amending EU legislation on medicinal products to ensure that water monitoring data communicated by water authorities are taken into account during the evaluation of MA applications and for post-reassessment of MA. Water monitoring data could be fed into the monograph system, if such a system is adopted.
19.1	Promoting/ requiring monitoring to collect data on the presence of medicinal residues in sewage sludge.
19.2	Amending the Sewage Sludge Directive to impose monitoring for selected pharmaceutical substances.
19.3	Cooperating with professionals to develop best practices guidance.
20.1	If the proposal for a Soil Framework Directive is adopted, it could be amended to address the issue of soil contamination by medicinal residues.

Legend*

Most promising actions
Actions suggested for primary intention (most feasible)

Most promising actions being of primary intention

*= please note that this is a very preliminary assessment resulting from a first screening of the options. A more detailed assessment of individual and combined actions would be required as a next step to better understand the advantages, shortcomings and thus the feasibility of these actions

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Annex 1: Usage of medicinal products in aquaculture – cases of Norway and the UK

Medicinal product class	Name of the active ingredient	Dosage used in aquaculture (mg active ingredient/kg fish)	Annual quantities used in aquaculture in Norway (kg)		Annual quantities used in aquaculture in UK (kg)	
Antibiotics/anti microbials	Amoxicillin	80-160 mg/kg during 10 days	0 in 2003 0 in 2004 0 in 2005	805 in 2003 340 in 2006	0 in 2003 0 in 2004 0 in 2005 55.2 in 2006	662 in 2003 5500 in 2006
	Florfenicol	10 mg/kg during 10 days	150.3 in 2003 83.08 in 2004 85.28 in 2005		0 in 2003 6 in 2004 10.2 in 2005 38.4 in 2006	
	Sulfadiazine trimetoprin	30-75 mg/kg during 5-10 days	-		-	
	Oxolinic acid	25 mg/kg during 10 days	252.4 in 2003 189.13 in 2004 188.4 in 2005		0 in 2003 0 in 2004 0 in 2005	

Medicinal product class	Name of the active ingredient	Dosage used in aquaculture (mg active ingredient/kg fish)	Annual quantities used in aquaculture in Norway (kg)		Annual quantities used in aquaculture in UK (kg)	
	Flumequin	25 mg/kg during 10 days	0 in 2003 0 in 2004 0 in 2005		0 in 2003 0 in 2004 0 in 2005	
	Oxytetracycline	50-125 mg/kg during 4-10 days	0.04 in 2003 1.16 in 2004 0 in 2005		662.8 in 2003 38 in 2004 1643 in 2005 5406 in 2006	
	Erythromycin	50-100 mg/kg during 21 days	0 in 2003 0 in 2004 0 in 2005		0 in 2003 0 in 2004 0 in 2005	
Microbicides/antiparasitics	Cypermethrin	5 µg/L for 1h bath and 15 µg/L for 30 min bath	62 in 2002 59 in 2003 55 in 2004 45 in 2005 49 in 2006	98 in 2003 132 in 2006	10.5 in 2003 657 in 2004 6.6 in 2005 9.7 in 2006	110 in 2003 26.5 in 2006
	Deltamethrin	2-3 µg/L for 40 minutes bath	23 in 2002 16 in 2003 17 in 2004 16 in 2005 23 in 2006		0 in 2003 0 in 2004 0 in 2005 0 in 2006	

Medicinal product class	Name of the active ingredient	Dosage used in aquaculture (mg active ingredient/kg fish)	Annual quantities used in aquaculture in Norway (kg)		Annual quantities used in aquaculture in UK (kg)	
	Emamectin benzoate	0.05 mg/kg during 7 days	20 in 2002 23 in 2003 32 in 2004 39 in 2005 60 in 2006		28.3 in 2003 52.6 in 2004 36.3 in 2005 16.8 in 2006	
	Azamethiphos	100 µg/L for 1h bath	0 in 2003 0 in 2004 0 in 2005 0 in 2006		35.5 in 2003 11.6 in 2004 0 in 2005 0 in 2006	
	Hydrogen peroxide	0.5 µg/L for 20 minutes bath	0 in 2003 0 in 2004 0 in 2005 0 in 2006		35.3 in 2003 43.8 in 2004 19.7 in 2005 0 in 2006	
	Teflubenzuron	10 mg/kg during 7 days	0 in 2003 0 in 2004 0 in 2005 0 in 2006		36 in 2003 0 in 2004 0 in 2005 0 in 2006	

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Annex 2: Examples of monitoring data in the environment

Medicinal products		Compartment			PNEC
		Groundwater	Surface water	Sediments	
Antibiotics	Amoxycillin	nd (degradation)	250 ng/L (river Taff, UK (Mompelat, 2009)) nd (Po river, Italy (Zuccato, 2005))		16 ng/L (Bergmann, 2011)
	Ofloxacin		60 ng/L (River Seine, France (Mompelat, 2009)) 37 ng/L (Po river, Italy (Zuccato, 2005))	10 ng/g (Valencian Community, Spain (Vazquez,2010)) 3 ng/L (Hernando, 2006)	115 ng/L (Bergmann, 2011)
	Ciprofloxacin		100 ng/L (Lake Leman, Switzerland[367]) 40 ng/L (River Seine, France (Mompelat, 2009)) 26 ng/L (Po river, Italy (Zuccato, 2005))	6 ng/g (Valencian Community, Spain (Vazquez,2010))	50 ng/L[367] 36 ng/L (Bergmann, 2011)
	Erythromycin	nd (German groundwater (GACE, 2007))	100 – 500 ng/L (German rivers (ter Laak, 2010) (GACE, 2007)) 15 – 30 ng/L (River Seine, France (Mompelat, 2009); Po river, Italy (Zuccato, 2005)) nd (UK rivers (WHO, 2011))	0 – 30 ng/L (Ebro river basin, Spain (Ferreira da Silva, 2011))	200 ng/L (Bergmann, 2011)
	Clarithromycin	nd (German groundwater[7])	50 – 950 ng/L (German rivers (ter Laak, 2010) (GACE, 2007)) 20 ng/L (Po river, Italy (Zuccato, 2005))	0 – 3 ng/L (Ebro river basin, Spain (Ferreira da Silva, 2011))	200 ng/L (Bergmann, 2011)
	Sulphamethoxazole	10 – 100 ng/L (German groundwater (GACE, 2007))	530 ng/L (River Seine, France (Mompelat, 2009)) 100 – 400 ng/L (German rivers (ter Laak, 2010) (GACE, 2007)) 50 ng/L (River Vartaa, Poland (Mompelat, 2009)) 15 ng/L (Lake Leman, Switzerland) nd (Po river, Italy (Zuccato, 2005); UK rivers (WHO, 2011))	80 ng/L (Germany (Ferreira da Silva, 2011)) 60 ng/L (France (Ferreira da Silva, 2011)) nd (Valencian Community, Spain[4])	20 000 ng/L(Roche, 2012) 600 ng/L (Bergmann, 2011) 200 ng/L (Kümmerer, 2008)
beta blockers	Atenolol	nd (German groundwater (GACE, 2007))	40 – 70 ng/L (German rivers (ter Laak, 2010) (GACE, 2007)) 42 ng/L (Po river, Italy (Zuccato, 2005)) ≈1 ng/L (French rivers (Vulliet, 2009))	0 – 3 ng/L (Ebro river basin, Spain (Ferreira da Silva, 2011))	10 000 000 ng/L(Roche, 2012) 100 000 ng/L (Bergmann, 2011)
	Propranolol	nd (German groundwater (GACE, 2007))	0 – 200 ng/L (German rivers (GACE, 2007)) 0 – 60 ng/L (UK rivers (WHO, 2011)) nd (French rivers (Vulliet,	2 ng/g (Valencian Community, Spain (Vazquez,2010))	1 800 ng/L (Kümmerer, 2008) 100 ng/L (Bergmann, 2011)

[367] Data from Service de la Protection de la Consommation, Genève

Medicinal products		Compartment			PNEC
		Groundwater	Surface water	Sediments	
			2009))		
	Metoprolol	0 – 30 ng/L (German groundwater (GACE, 2007))	250 – 1000 ng/L (German rivers (GACE, 2007)) nd (French rivers (Vulliet, 2009))	7 ng/g (Valencian Community, Spain (Vazquez,2010))	7 000 ng/L (Kümmerer, 2008) 3 200 ng/L (Bergmann, 2011)
Lipid regulators	Bezafibrate	20 – 100 ng/L (German rivers (GACE, 2007))	100 – 300 ng/L (German rivers (ter Laak, 2010) (GACE, 2007)) 3 ng/L (Po river, Italy(Zuccato, 2005))	nd (Ebro river basin, Spain (Ferreira da Silva, 2011))	100 000 ng/L(Roche, 2012) 1 200 ng/L (Bergmann, 2011)
analgesics/anti-inflammatory medicinal products	Paracetamol		1400 ng/L (river Taff, UK (Mompelat, 2009)) 75 ng/L (Hérault watershed, France (Mompelat, 2009))		1 000 ng/L (Bergmann, 2011)
	Ibuprofen	0 – 200 ng/L (German groundwater (GACE, 2007))	40 – 800 ng/L (UK rivers (Mompelat, 2009) (WHO, 2011)) 50 – 100 ng/L (German rivers (Mompelat, 2009) (ter Laak, 2010) (GACE, 2007)) 17 ng/L (Po river, Italy (Zuccato, 2005))	0 – 20 ng/L (Ebro river basin, Spain (Ferreira da Silva, 2011)) nd (Valencian Community, Spain (Vazquez,2010))	5000 ng/L[368],(Roche, 2012) (Bergmann, 2011)
	Salicylic acid		30 ng/L (river Taff, UK (Mompelat, 2009))		200 000 ng/L (Bergmann, 2011)
	Diclofenac	60 – 400 ng/L (German groundwater (GACE, 2007)) 400 ng/L (French groundwater (KNAPPE, 2008))	200 – 500 ng/L (German rivers(Mompelat, 2009) (ter Laak, 2010) (GACE, 2007)) 2 ng/L (Hérault watershed, France (Mompelat, 2009); French rivers (Vulliet, 2009))	400 ng/L (max in Germany (Ferreira da Silva, 2011)) nd (Greifensee lake, Switzerland (Buser, 1998); Valencian Community, Spain (Vazquez,2010))	100 000 ng/L[368] 10 000 ng/L (Roche, 2012) 6 000 ng/L (Kümmerer, 2008) 100 ng/L (Bergmann, 2011)
anti-epileptic medicinal products	Carbamazepine	200 – 1000 ng/L (German groundwater (GACE, 2007)) 20 ng/L (French groundwater (KNAPPE, 2008))	500 – 1500 ng/L (German rivers (ter Laak, 2010) (GACE, 2007)) 45 ng/L (Lake Leman, Switzerland[369]) 34 ng/L (Po river, Italy (Zuccato, 2005))	1 000 ng/L (Germany (Ferreira da Silva, 2011)) 70 ng/L (France (Ferreira da Silva, 2011)) 5 ng/g (Valencian Community, Spain (Vazquez,2010))	2 500 ng/L[369] (Kümmerer, 2008) 25 000 ng/L (Roche, 2012)
X-ray contrast media	Iomeprol	0 – 160 ng/L (German groundwater (GACE, 2007))	100 –500 ng/L (German rivers (ter Laak, 2010) (GACE, 2007) (Ternes, 2000))		n/a
	Iopamidol	100 – 2000 ng/L (German groundwater (GACE, 2007) (KNAPPE, 2008))	200 –1000 ng/L (German rivers (ter Laak, 2010) (GACE, 2007) (Ternes, 2000))	1 400 ng/L (max found in Germany (Ferreira da Silva, 2011))	n/a
	Iopromide	0 – 40 ng/L (German groundwater (GACE, 2007))	50 –500 ng/L (German rivers (ter Laak, 2010) (GACE, 2007) (Ternes, 2000))	500 ng/L (Wickerbach creek, Germany (Loefler, 2005))	100 000 ng/L[369] 7 000 000 ng/L (Bergmann, 2011)

Legend: nd - not determined

[368] Data from the Swedish Monitoring Programme (2005)

[369] Data from Service de la Protection de la Consommation, Genève

Annex 3: Case studies on specific medicinal products

Seven case studies of active substances used in medicinal products for both humans and animals are presented hereafter. The active pharmaceutical ingredients of interest were selected in agreement with the EAHC. These case studies illustrate some scientific characteristics for each of active pharmaceutical ingredient and procedural information. The selected active substances include:

- Doramectin (veterinary use);
- Ethinylestradiol (oral contraceptive and patch - human use);
- 5 Fluorouracil (human use);
- Fluoxetine (human use);
- Ivermectin (veterinary use);
- Tetracycline (veterinary use); and
- Tylosin (veterinary use).

Doramectin

Active substance and product information

Doramectin is an antiparasitic agent belonging to the group of avermectins (including Ivermectin[370]), fermentation products from a strain of *Streptomyces avermitilis* possessing potent anthelmintic[371] and insecticidal activities (Kolar, 2008). They are the most used agents in veterinary medicine for several years in the prevention of parasitic diseases. The relative popularity of the avermectins amongst farmers and veterinarians can be attributed to their spectrum of activity, convenience and wide margin of safety to the targeted animals. Key medicines containing Doramectin include:

- Prontax 5mg/ml® pour-on solution for cattle: the product is indicated for treatment of gastrointestinal roundworms, lungworms, eye worms, warbles, sucking and biting lice, mange mites and horn fly in cattle.
- Prontax 10 mg/ml® solution for injection for cattle, sheep and pigs (associated name: Dectomax 10 mg/ml).

370 www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/referrals/Prontax_10_33vet_referral_000059.jsp&mid=WCobo1ac058009861a1

371 agent that destroys or causes the expulsion of parasitic intestinal worms

Scientific information

Environmental aspects

Contamination pathway and behaviour in environment

The use of Doramectin can result in the release of residues in the treatment sites, where animal waste is disposed of and in areas receiving run-off. The faeces are the major route of excretion of Doramectin in pigs, cattle, dog, and rat. For instance, in pigs, 20% of the dose is excreted within 21 days in faeces compared to <1% in urine (Heitzman, 1996). Excretion of potentially toxic levels of Doramectin for dung fauna may take place over a period of several weeks. Pfizer (Pfizer, 1996) showed that the concentration of total Doramectin residues excreted in the faeces of cattle (treated with 500 µg of Doramectin/kg of bodyweight) peaked at 21 days after administration (156 and 270 µg/kg for females and males respectively) and declined thereafter (Pfizer, 1996), accounting for 52 µg/kg at 35 days and 3.9 µg/kg at 56 days (EMEA, 2007). The total dose excreted over 56 days was 36% for female and 39% for male cattle.

The products of Doramectin metabolism are similar in pigs, cattle, dogs, and rats (radiolabelled product) (Heitzman, 1996). The following metabolites were identified in the liver and faeces from each analysed species and in the fat of cattle: unchanged Doramectin, 3"-O-desmethyl Doramectin, 24-hydroxymethyl Doramectin, and 24-hydroxymethyl-3"-O-desmethyl Doramectin (IPCS, 2006). In the Scientific discussion about Prontax 5mg/ml, it is highlighted that the parent medicinal product could account for 79% of the total radioactive faecal residues excreted (EMEA, 2007).

Once released in the environment, all avermectins are highly insoluble in water. According to a Safety Data Sheet on Dectomax® (equivalent to Prontax®), Doramectin is expected to bind tightly to soil or sediment and readily adsorb to it. It is unlikely to reach groundwater and is also biodegradable by soil micro flora (Pfizer, 2009).

Exposure

Dung fauna and aquatic organisms are exposed to Doramectin through the presence of residues from the excretions (faeces) of treated animals in soils and water. However, only insignificant amounts of Doramectin are expected to partition into surface waters in runoff from a feedlot due to the strong sorption of medicinal product to cattle faeces. Predicted Environmental Concentrations (PEC) were estimated in the ERA dossier for Prontax 5mg/ml®. PEC for surface water was estimated at 0.0026 µg Doramectin /l surface water in the case of a run-off scenario and at 0.5225 µg Doramectin /l surface water in case of direct excretion into water. These PECs were refined later on (e.g. using the FOCUS model as recommended by CVMP guideline CVMP/ERA/418282/2005 (EMA, 2007)), but related risk quotients remained > 1 in any cases.

More marginally, medicinal product exchange may also occur through self-licking between animals. It was shown that the total amount of medicinal product ingested by all non-treated cattle could represent 29% of the total amount of Doramectin poured on the backs of treated animals (Bousquet-Mélou, 2004).

Impacts

Several studies showed that residues of Doramectin or its metabolites in faeces of livestock may have adverse effects on non-target organisms (WHO, 2004), in particular on dung-dwelling organisms (Kolar, 2008).

Kolar et al. (2008) observed EC50s for the effect on reproduction of springtails and enchytraeids of 42 and 170 mg/kg for Doramectin. When exposed in faeces, springtails and enchytraeids gave LC50s and EC50s of 2.2 and 2.4 mg/kg. Furthermore, LC50 of 1.34 µg/kg soil for horn flies (*Haematobia irritans*) and a NOEC of 4.0µg/kg soil for dung beetles (*Ontophagus gazelle*) were reported in the CVMP Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet of Prontax 5mg/ml (EMEA, 2007). For earthworms, NOEC for effects on body weight was 8.4 mg/kg, but reproduction was not affected. This study indicates a potential risk of avermectins for soil invertebrates colonising faeces from recently treated sheep (Heitzman, 1996). Endpoints in aquatic species include (Pfizer, 2006b):

- LC50 *Onchorhynchus mykiss* (rainbow trout) 5.1 ppb/96 hr, static
- LC50 *Lepomis macrochirus* (bluegill sunfish) 11 ppb/96 hr, static

An EC50 of 0.1 µg/L and a NOEC of 0.025 were also derived from a toxicity study of Doramectin in *Daphnia* (*D. magna*) (EMEA, 2007).

Doramectin is very toxic to dung fauna and aquatic organisms (Irish Medecine Board, 2012).

- **Human exposure through consumption of food of animal origin**

Humans are not exposed to Doramectin through milk consumption since treating lactating cows used to produce milk is forbidden in the Marketing authorisation (Pfizer, 2009). Similarly, although Doramectin residues may accumulate in muscular tissue (Moreno, 2008) and fat (IPCS, 2006) of animal destined to consumption, human exposure through meat consumption is unlikely because of the mandatory withdrawals periods of animals after the substance injection (EMEA, 2007). In any case, it has been shown that penetration of the blood brain barrier by avermectins is extremely poor.

Procedural aspects, ERA and risk mitigation options

ERA were performed for both Prontax 10mg/ml® for injection and Prontax 5mg/ml® for pour-on, and referrals were presented during the authorisation procedure on environmental grounds on both cases.

- **Prontax 10mg/ml® for injection**

Prontax 10mg/ml® solution for injection for cattle, sheep and pigs was submitted to EMA following a decentralised procedure, in the framework of Article 32 of Directive 2001/82/EC, as amended. The reference products for this generic application were Dectomax 1% w/v® solution for injection for cattle and sheep and Dectomax 10 mg/ml® solution for injection for pigs. The RMS was Ireland. CMS include Austria, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Latvia, Lithuania, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden as CMS, as well as Iceland and Norway. DE was not included in the decentralised procedure itself but later within the referral process, DE

was involved as peer reviewer. Information of the historic of the procedure and of the referral for environmental matters is publicly available on EMA website[372].The decentralised procedure started on 26 February 2010.

An ERA was performed by the applicant in accordance with the VICH guidelines for Phase I and Phase II assessment adopted by the CVMP (EMA, 2000) (EMA, 2004) as well as the CVMP guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH Guidelines GL6 and GL38 (EMA, 2007) . The ERA for pigs could stop at Phase I in accordance with the VICH guideline. However, a Phase II, Tier A assessment was required for cattle and sheep.

During the critical review of the dossier, potential serious risks were identified by two CMS (the Netherlands and France) regarding the Environmental Risk Assessment and by the Netherlands regarding the proposed withdrawal period for cattle. On 26 April 2011, the RMS, Ireland, referred the matter to the Committee for Medicinal Products for Veterinary Use (CVMP) pursuant to Article 33(4) of Directive 2001/82/EC.

Details of why ERA was judged insufficient are provided in the Annex II to the EPAR. Main issues debated in the referral included:

- the determination of the n-octanol/water coefficient using the shake flask method, whereas this method is not considered suitable for substances with a octanol/water coefficient (logPow) above 4;
- absence of bioaccumulation study and assessment of secondary poisoning;
- absence of data on the nature and rates of metabolites are available, which prevents the calculation of refined PEC based on metabolism;
- Risk Quotient calculated for dung insect would call for a Tier B assessment, but no harmonised guidance on how to conduct Tier B assessment studies for dung insects is currently available. This therefore calls for the implementation of precautionary measures.

To our knowledge, it does not seem that complementary information was submitted by the applicant in response to this critical review.

In its scientific conclusions to the referral from the Netherlands and France, the CVMP states that *"in terms of environmental safety, the current data package did not allow to rule out bioaccumulation of Doramectin and a risk to the aquatic compartment had been identified based on available toxicity data (acute toxicity for Daphnia magna) as well as a risk to dung fauna exposed to residue-containing dung when the product is used in accordance with the recommended posology. Therefore, appropriate risk mitigation measures are considered necessary, as specified in the product information".*

A positive decision by the EC on the marketing authorisation of this product was issued on 25 May 2012, provided the implementation of RMM. In accordance with VICH Phase II guidance

372 www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/referrals/Prontax_10_33/vet_referral_000059.jsp&mid=WCobo1ac05805c5170

RMMs have to be imposed if a risk for the environment still exists at the end of Phase II Tier B "the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority". For this application a Phase II Tier B was requested but is still missing (see Annex II for Prontax at EMA page), thus RMMs were imposed without the guideline conform Tier B assessment.

Risk mitigation measures consist in including warning sentences within the SCP sections "4.5. Special precautions for use" and "5.2. Environmental properties" (Heitzman, 1996), respectively:

"Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments. The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of Doramectin (and products of the same anthelmintic class) in cattle and sheep. The risk to aquatic ecosystems will be reduced by keeping treated cattle away from water bodies for two to five weeks after treatment".

"Like other macrocyclic lactons, Doramectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of Doramectin may take place over a period of several weeks. Faeces containing Doramectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms that may impact on the dung degradation. Doramectin is very toxic to aquatic organisms and may accumulate in sediments".

- **Prontax (Dectomax) 5mg/ml® pour-on solution**

The applicant *Pfizer Limited* has submitted an application for a decentralised procedure for Dectomax 5 mg/ml pour-on solution for cattle. The RMS was Ireland and the CMS were Austria, Bulgaria, Denmark, Spain, Finland, France, Hungary, Iceland, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia and Sweden. The application was submitted in accordance with the Article 13(1) of the Directive 2001/82/EC (i.e. an application for a generic product). The reference product for this generic application was Dectomax 5 mg/ml pour-on solution for cattle. An ERA for this product was conducted by Pfizer Inc in 1996 and revised in 2002(Pfizer, 1996).

Similarly to Prontax 10m/ml®, there was disagreement between the RMS and CMS on the data presented to support the Environmental Risk Assessment during the procedure, although no referral was made on the withdrawal period. Once again, France and the Netherlands considered that the authorisation of Prontax 5 mg/ml® pour-on solution for cattle may present a potential serious risk to the environment, for the same reasons as those presented for Prontax 10mg/ml®. There again, the EC decided to authorise the marketing of this product provided the implementation of risk mitigation measures (same as for Prontax 10mg/ml®).

Ethinylestradiol

Active substance and product information

Ethinylestradiol (EE2) is a synthetic derivative of the natural hormone estradiol and belongs to the pharmacologic group "estrogens". It is contained in the majority of available oral contraceptive products, in combination with a Progestagens.

EE2 is used worldwide for female contraception. Some oral contraceptives (e.g. Beyaz®, Yaz®) also are used to relieve the symptoms of premenstrual dysphoric disorder (physical and emotional symptoms that occur before the menstrual period each month) in women who have chosen to use a contraceptive to prevent pregnancy. As well as contraception and menstrual disorders, Ethinylestradiol is also used as a second line therapy for preventing postmenopausal osteoporosis and female hypogonadism. Approximately 8.1% of women (or 4.1% of the total population) in the United States would use EE2 as a contraceptive. This use is expected to be much higher in the EU (Hannah, 2009). Based on 2001 sales, 628.7kg of Ethinylestradiol was sold in the EU (EMEA, 2005). EE2-based medicines only are delivered under prescription.

- EE2 is mostly administered orally but can also be administered through patches. Examples of oral medicines include:
- Mibelle® 30 micrograms/150 micrograms Film-Coated Tablets (MHRA, 2011) (SFT, 2006): combined oral contraceptive pill that contains both estradiol (30 micrograms) and levonorgestrel (150 micrograms).
- Ethinylestradiol/Gestodene 30/75 "Stragen"®[373] (EMEA, 2008) (The product is a generic of Meloden and Gynera coated tablets)
- Drospirenone/Ethinylestradiol film-coated tablets (Example of a marketed product: Kylixa® (National Institute of Pharmacy, 2012); yvidually®[374] (or Flexyess®), which is an 'extended use' oral contraceptive, which means that it can be taken daily for up to 120 days. It contains 3 mg of drospirenone (DRSP) + 20 micrograms of Ethinylestradiol (EE)

The amount of EE2 contained in these oral contraceptives generally range from 20 to 35 micrograms. These products must be taken daily for at least 21 days each month. Some can be taken much longer, such as new products like Flexyess®, which can be taken 120 days in a row.

EVRA® is an example of trans-dermal medicine, in the form of trans-dermal patch containing 0.75 mg of EE2 that is used as one patch per week for three weeks followed by a fourth week, which is patch-free. The patch is applied to the buttock, abdomen, upper arm or upper back. The package includes an appropriate disposal container for used patches.

Scientific information

Environmental aspects

Contamination pathway and behaviour in environment

- Oral contraceptives

The main contamination pathways from oral contraceptives is the excretion through urines of their active pharmaceutical ingredient EE2 or its conjugate in the sewage network and the

373 mri.medagencies.org/Human/Product/Details/15561

374 www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Yvidually/human_referral_000304.jsp&mid=WC0b01ac058024e99

discharge of remaining active substances and/or its conjugate contained in treated wastewater or sludge into the natural environment. This differs from the administration of EE2 through patches (e.g. EVRA®) for which disposal is the main environmental contamination pathway (see below). EE2 undergoes biological transformation in the body (Bolt, 1979) (Guengerich, 1990). EE2 excretion rates are extremely high and reported to be up to 85%, with the majority (50 to 90%) being excreted in conjugated form together with urine (Ranney, 1977). At this rate, at least circa 6 micrograms per treated women are released every day in sewage waters (based on a pill containing 20mg estradiol taken 21 days a month). If it is taken without interruption, this amount reaches 8.5 micrograms/day/capita. Given that STPs are expected to remove some EE2 and because some dilution and in-stream depletion occurs in most receiving waters most of the time, almost all surface waters would be expected to have considerably lower EE2 concentrations (Hannah, 2009). This does not mean that EE2 is eliminated from the environment. It indeed may be removed from the water compartment through its significant adsorption to sludge (Ternes, 2002). If the efficiency of WWTPs to prevent natural and synthetic estrogens from entering the environment remains unchanged, the quantity of EE2 and conjugates that is released to water bodies is unlikely to decrease, due to their origin and use. Thereby, the persistence of EE2 is extremely high (Maes, 2011).

- Patches

As for oral contraceptives, contamination can occur through the release of urine and faeces into the sewage system. However, the main contamination pathway is rather considered to be the improper disposal of used patches: the patch was designed to administer 20 µg of EE2 per day, which means that approximately 80% of EE2 is not absorbed and remained in the used patch (i.e. 610 µg of EE2). The manufacturer agreed to include in the package an appropriate disposal container for used patches. So far, no leak from these containers to be disposed of with household waste has been reported, but analyses of patients' compliance with these disposal practices were not available. EE2 is transported over long distances and persists in the environment (Kuch, 2001).

▷ **Exposure**

Hannah et al. (2009) showed that even assuming no removal in the STP and no dilution in the receiving water occur, long-term EE2 concentrations in typical surface waters are unlikely to be beyond 9 ng/L in Europe. Taking into account both factors, they show that maximum low-flow PECs amounts 1.3 ng/L for Europe, based on predicted concentrations from the PhATE and GREAT-ER models, although an assessment of oestrogen removal efficiency for WTW in the UK showed simple biological plants to be poor with only about 30% removal (Johnson, 2007). In 2003, the PEC in surface water was estimated at 2.28ng/l in the EU (EMEA, 2005).

These estimates are in line with field observations. EE2 has been detected in sewage treatment plant effluents in low nanogram-per-litre (ng/l) levels and occasionally also in surface waters and drinking water in e.g. the United States, UK, Canada, Brazil, Germany (Caldwell, 2008).

The market introduction of EVRA® was estimated to possibly increase EE2 PEC in surface water to 2.43 ng/L (EMEA, 2005), should no mitigation actions be taken to avoid environmental contamination from patches, leading to an increased environmental exposure.

Fauna is exposed to EE2 through the presence of EE2 in sludge and aquatic environment. Rainbow trout (O.mykiss) and roach (Rutilus rutilus) exposed to treated sewage effluent in

controlled continuous-flow tanks concentrated EE2in the bile — at levels beyond endogenous production, with bioconcentration ranging from 4,000 to 6,000 for EE2 (Daughton, 2011). Predators can also be exposed through EE2 potential for food chain transfer starting at the basis of the web (Maes, 2011). Al-Ansari et al. (2010) have detected Ethynylestradiol EE2 in wild fish collected downstream of Canadian municipal effluents at average concentration of 1.5 ng/g. The authors suggest that EE2 could be a potential candidate for bioaccumulation in higher predators, especially bottom feeding fishes. In this context, Maes (2011) reported a BCF of 960 L/kg ww for male zebrafish and showed that dietary applied EE2 glucuronide, synthesised by chironomids, can be reconverted to the parent compound in predator fish (Al-Ansari, 2010), as highlighted in Daughton et al. (2011).

▷ Impacts

The mode of action of EE2 is receptor-mediated, and estrogen receptors are highly conserved in structure and function across species, in mammals and other vertebrates. Numerous studies investigated potential effects of EE2 on aquatic organisms, and the oestrogenic effects of WTW effluent ascribed to Ethinylestradiol have been recognised for two decades (Montagnani, 1996) (Purdom, 1994). Negative impacts of EE2 at low level (0,1ng/l) have been observed on fish, with lethal effects at higher concentrations (5ng/L) (Kime, 1999). Based on a literature review, Caldwell et al. (2008) showed that the median hazardous concentration at which 5% of the fish species tested were affected by EE2 amounts 0.35 ng/L. Effects from EE2 have also been documented at the sub-ppt level in surrounding water (i.e., 0.05 ng/L) (Larsen, 2008). Negative impacts include changes in gender ratio and reduced species reproduction in exposed fish populations at environmentally realistic concentrations (Nash, 2004) (Jobling, 2003) (Kapstein, 2005) . This was identified as the most sensitive end point in aquatic species (Caldwell, 2008). EE2 was classified as a mere baseline toxicant of low toxicity in algae (Fent, 2006), although it can highly concentrate 14C-EE2 (72 h Calgae/Cwater: 2200 L/kg ww) (Maes, 2011).

Depending on the route of exposure (water or ingestion), organisms can eliminate EE2 more or less rapidly. It was shown that EE2 was considerably slower eliminated when fish had been exposed via the water (t1/2: 53 h) than after dietary ingestion of living prey containing hydrophilic EE2 metabolites (t1/2: 30 h) (Kapstein, 2005).

Bergmann et al. (2011) summarised the possible risk represented by EE2 for the aquatic environment through the calculation of a risk quotient (PEC/PNEC ratio) of almost 10 000.

▶ Human health

Humans can be indirectly exposed in the long run to low concentrations of EE2 through drinking water and fish consumption. It has to be noted that EE2 is more bioavailable with the patch than with an oral contraceptive (Kapstein, 2005). However, in the US, Caldwell et al. (2010) concluded that prescribed and total estrogens that may potentially be present in drinking water in the United States are not causing adverse effects in US residents, including sensitive subpopulations. Levels of EE2 in drinking water are reported as inferior to 1 ng/L (Webb, 2003), which may be considered negligible compared with a dietary intake of steroids estimated at 0.1 mg/day. A dietary comparison in the US indicates that potential exposures to trace levels of total estrogens (whether from a prescribed or naturally occurring source) predicted to be in drinking water in the United States are at least 82 times lower than exposures from background concentrations of

naturally occurring estrogens in the diet. Yet, to our knowledge, no human exposure studies have been conducted on EE2 residues in wild fish. Daughton et al. (2011), however, point out that tissue residues of certain APIs in aquaculture fish can resist degradation during cooking and can migrate from one tissue to another during cooking. In Mibelle® EPAR, it is acknowledged that sex steroids can promote the growth of certain hormone-dependent tissues and tumours, but to our knowledge, no effects of human exposure through the environment were reported.

Procedural aspects, ERA and risk mitigation options

- **Oral contraceptives**

Most oral contraceptives currently placed on the market are generics, derived from long-term commercialised medicines. Medicinal products containing EE2 are in general presented for a decentralised procedure, which allows these products to be extensively placed on the market in the EU. In this cases, marketing authorisation (MA) is granted without ERAs sometimes with the commitment of MA holders to perform ERA *a posteriori* within 6 months after approval, as in the case of Mibelle. In this case, ERA dossiers could not be retrieved on the UK Medicines and Healthcare products Regulatory Agency (MHRA's website).

Table 21: Non-exhaustive list of oral contraceptives containing EE2 and corresponding procedures for Marketing authorisations

Mibelle® 30micrograms/150micrograms Film-Coated Tablets	Decentralised procedure RMS: UK CMS: Austria, Belgium, Czech Republic, Germany, The Netherlands, Poland and The Slovak Republic	Market authorisation delivered on the 15 March 2010 The reference medicinal product for this application is Microgynon 30 0.03 to 0.15mg sugarcoated tablet licensed to Bayer plc. In the UK on 18th November 1973.	No reference to a potential environmental impact taking into account. The medicinal product is a generic. The reference product has been in use for many years and the safety profile of the active substances is well established. The Marketing Authorisation Holder has provided a commitment that an ERA for Ethinylestradiol and levonorgestrel will to be performed within 6 months after approval.	No	PAR accessible through the Medicines and Healthcare products Regulatory Agency (MHRA) in UK (MHRA, 2011) ERA not available
Ethinylestradiol/Gestodene 30/75 "Stragen" ®	Decentralised procedure RMS: Denmark CMS: the Netherlands, Italy, Luxembourg and Belgium	The decentralised procedure was finalised the August 13th, 2008 and the product was authorised on 2 October 2008. The date for the renewal will be the August 13th, 2013 The reference products for this application are Meloden and Gynera coated tablets, registered in Denmark since 1995 and 1988 respectively)	No ERA could not be found but the public assessment report states that: "The approval of this product will not result in an increase in the total quantity of gestodene/Ethinylestradiol released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal".	No	PAR is available on the Heads of Medicines Agency website (EMEA, 2008) . No reference can be found via the Danish Health and Medicines Authority (DHMA) as the competent authority involved in the assessment of the product.

Drospirenone/Ethinylestradiol film-coated tablets Example of a marketed product; Kylixa®	Decentralised procedure RMS: Hungary CMS: according to the product but for the kylixa example, the CMS are Belgium, Germany, Luxembourg, The Netherlands and Sweden	The procedure started the August 3rd, 2011 and ended by an approval the September 2nd, 2011 The combination of Drospirenone and Ethinylestradiol was already approved for use in other oral contraceptives: Yasmin (NL license RVG 23827), containing 3 mg DRSP and 30 µg EE, and Yasminelle (NL license RVG 31781), containing 3 mg DRSP and 20 µg EE, for which first marketing authorisations were granted in 2000, with the Netherlands as RMS. The marketing authorisation has been granted based on article 8(3) of Directive 2001/83/EC: a full application containing known active substances.	The public assessment report states, "Since the film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary".	No RMM have been identified for the products as no safety concerns have been identify for the reference product (Yasminelle film - coated tablets)	PAR (National Institute of Pharmacy, 2012)
Yvidually® (or Flexyess®), Drospirenone/Ethiny	Decentralised procedure RMS: Netherlands	Authorisation granted on 19 April 2012	No ERA mentioned in PAR.	No RMM mentioned	PAR (EMEA, 2012)

lestradiol combination	CMS: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Germany, Greece, Finland, France, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom

Case of Evra®

The case of Evra®, which required the submission of an ERA, is presented below.

Evra was presented in 2001 following a centralised procedure. The initial procedure started on 12 of March 2001, and the marketing authorisation was delivered on 22 of August 2002. The competent authorities in charge of the assessment were the European Agency for the Evaluation of Medicinal Products and the Committee for Proprietary Medicinal Products (CPMP). Since the issuance of marketing authorisation, it has been renewed two times - on 07/09/2007 and on 15/06/2012[375]. Information relative to this procedure is available on the EMA website within the European Public Assessment Report (EPAR). EPAR was first published on 21/10/2005 and last updated on 06/04/2009. Several other documents can be found on the same website such as the scientific discussion (Bolt, 1979), the procedural steps taken before authorisation[376] and steps taken/scientific information after authorisation[377].

An ERA was performed as part of the Marketing authorisation although it was not mandatory at the time. It is in line with HMP guidelines developed *a posteriori* by ECHA although they were not published yet. It corresponds to a complete Phase I assessment. PEC for surface water being below 0.01 µg/l, a Phase II assessment was not warranted. No revision of environmental information is specified in the "Procedural steps and scientific information after authorisation" (Al-Ansari, 2010) following the publication of ERA guidelines in December 2006.

During its meeting on the 19 to 21 March 2002 and following the comments received by independent environmental researchers, the CPMP agreed on the necessity to evaluate potential risks and environmental implications of the disposal of the product. On the 2 April 2002, the applicant submitted supplementary information on the environmental risk analysis regarding concerns about the disposal of Evra. ERA then concluded that there is a negative impact on the environment from the use of Evra patch if inappropriately disposed, due to the release of Ethinylestradiol in fresh water. PEC surface water was calculated based on the amount of wastewater per inhabitant per day, which is in line with the ERA guidelines for human medicinal products. As mentioned in the section "environmental exposure", the reference in the scientific discussion stipulates that the PEC surface water at the time was 2.28ng/L. The total amount of Ethinylestradiol released into environment through its presence into Evra patch was estimated to lead to an increase of up to 2.43 ng/L. The results of ERA are summarised in the scientific discussion report of Evra (Bolt, 1979). Only the PEC in surface water is provided, with indications of possible effects on fish at 0.1 and 5 ng/l.

According to the pharmaceutical legislation in place, the ERA was not a criterion to be taken into account in deciding the potential granting of a marketing authorisation. It however foresees that

375 Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considered that the benefit-risk balance of EVRA for female contraception indication remained positive and therefore recommended the renewal of the marketing authorisation with unlimited validity.
376 www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_before_authorisation/human/000410/WC500031509.pdf
377 www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000410/WC500031511.pdf

risk mitigation measures could be implemented. The authorisation decision therefore was accompanied by recommendations regarding the product disposal, which have been included in the relevant section of the SPC: "The applicant agreed to include in the package an appropriate disposal container for used patches prior to marketing the product in the European Union". Since 2003, the product has been sold along with specific disposal containers. These containers can then be disposed of with household waste. However, no indication is provided on the users' compliance with this risk mitigation measure.

Fluorouracil

Active substance and product information

Fluorouracil (CAS 51-21-8 5) is anti-neoplastic anti-metabolite that is used for the palliative treatment of a number of malignancies, both as a single agent and in combination with other agents and radiotherapy (Longley, 2003). Fluorouracil is also available as a cream for treatment of malignant and non-malignant skin conditions. Products containing this active substance are prescription only medicines. Examples of medicines include:

- Actikerall® 5 mg/g + 100 mg/g (cutaneous solution)
- Fluorouracil® 50mg/ml Solution for Injection or Infusion. The selection of an appropriate dose and treatment regime depend upon the condition of the patient, the type of carcinoma being treated and whether Fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1gram.
- Xeloda®, Filmdragerad tablett 150 mg, containing Capecitabin, pro-drug of 5-Fluorouracil (oral administration)

Scientific information

Environmental aspects

Contamination pathway and behaviour in environment

Fluorouracil's production and use as an anti-neoplastic may result in its release into the environment through various contamination pathways[378], from its manufacture through its use and to its disposal. In addition to possible releases during its production and disposal, it can be excreted by patients through urine and/or the respiratory system. The primary route of elimination is respiratory (approximately 90% as carbon dioxide). The secondary route is renal. Given by continuous iv infusion for 24 hr, urinary excretion of Fluorouracil is only 4% (approximately 7 to 20% remain unchanged; with 90% excreted within the first hour). Fluorouracil is anticipated to be one of the compounds present in hospital effluent (Kümmerer, 2001). Fluorouracil was assigned a mean theoretical sewage concentration of 2.03 µg/L in the wastewater of a large university hospital based on its use pattern (Hartmann, 1998). However, it could not be detected in the corresponding studies.

378 NCBI Fluorouracil - Compound Summary (CID 3385). Available at: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3385#x351

Fluorouracil does not persist in the environment[379] (Straub, 2010). In soils and water, biodegradation is an important environmental fate process (Kiffmeyer, 1998) (Straub, 2010) with 100% biodegradation occurring within 5 to approximately 10 days. Excreted 5-Fluorouracil has been shown to be rapidly degraded in both sewage works and surface waters (Hoffmann LaRoche, 2006) (Hoffmann LaRoche, 2005) (Straub, 2010). 5-Fluorouracil is likely to volatise at ambient temperature (CRAMIF, 2011). In air, Fluorouracil will exist in both the vapour and particulate phases in the atmosphere. Vapour-phase Fluorouracil will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. Half-life in air is estimated to be 3 days[380]. Furthermore, an estimated Bioconcentration factor (BCF) of 3 suggests the potential for bioconcentration in aquatic organisms is low.

▷ Exposure

Exposure to the environment of Capecitabine, pro-drug of 5-Fluorouracil, is considered very limited, and therefore no risk of concern would be expected (EMEA, 2005b). No specific exposure data could be found on Fluorouracil in publicly available sources through any administration route.

▷ Impacts

Table 22 presents results of ecotoxicological studies on 5-FU.

Table 22 : results of ecotoxicological studies on 5-FU (Straub, 2010)

Test organisms			
Cyanobacteria (*Anabaena flos-aquae*)	NOEC 72 h	2 µg/l	OECD 201
Water-flea (*Daphnia magna*)	NOEC 21 d	2.8 µg/l	OECD 211
Zebrafish (*Danio rerio*)	NOEC 35 d	32 000 µg/l	OECD 210
Micro-organisms	NOEC	1000 000 µg/l	activated sludge respiration inhibition

Low sensitivity to the effects of 5-Fluorouracil was revealed in fish (*Danio rerio* and *Lebistes reticulatus*) in survival tests and in crustacean *Daphnia magna* in immobilisation test (Załęska-Radziwiłł, 2011).

The substance is not considered a carcinogen or genotoxic at low concentrations, but developmental or reproductive toxicity was reported in laboratory animals (Straub, 2010). Although Straub (2010) reported a Daphnia NOEC of 2.8 µg/l, a lowest NOEC was obtained in the reproduction test on *Daphnia magna* (0.00006 mg/l) in Załęska-Radziwiłł et al. (2011). Medicinal products that inhibit DNA, RNA, and protein synthesis like Fluorouracil indeed might be expected to have adverse effects on gametogenesis (McEvoy, 2007). 5-Fluorouracil resulting from

379 HSDB database: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+51-21-8

380 If released to air, an estimated vapor pressure of 2.7X10-6 mm Hg at 25 deg C indicates fluorouracil will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase fluorouracil will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 3 days. Source: HSDB database. See: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+51-21-8

conversion of capecitabine has been found to target male and female reproductive organs (EMEA, 2005b).

- **Human health**

Exposure to Fluorouracil among the general population may be limited to those administered the medicinal product, an antineoplastic and to occupational exposure. To our knowledge, no data is available on potential effects of environmental exposure on human health.

Procedural aspects, ERA and risk mitigation options

Table 23 presents details of procedures for examples of medicinal products containing Fluorouracil. Except for Xeloda®, which contains Capecitabin, a pro-drug of 5-Fluorouracil, it seems that no ERA was performed.

The assessment conducted by the University of Warsaw (Załęska-Radziwiłł, 2011), using EMEA Guidelines, revealed high risk to aquatic animals for 5-Fluorouracil (RQ>5). However, based on the Straub (Straub, 2010) and Fass assessment in Sweden[381], except for the EMEA Phase I default PEC, the risk characterisation of Fluorouracil by PEC:PNEC and MEC:PNEC ratios for various environmental compartments resulted in no significant risk. As the EMEA Phase I PEC does not integrate documented human metabolism and environmental degradation, in contrast to refined PEC derivations, it is inferred that the current use of CAP and 5-FU does not present any evident risk to the environment. An additional evaluation of persistence, bioaccumulation, and toxicity (PBT) properties supports the conclusion of no significant environmental risk for 5-FU and CAP.

381 PEC/PNEC =0.000828/0.2 = 0.0414 for 5FU, which means that the phrase 'Use of the medicine has been considered to result in insignificant environmental risk.' is used for Level 1 and 2.
www.fass.se/pdfprint/servlet/se.lif.fass.pdfprint.servlets.ConvertServlet?nplId=20010202000030&docTypeId=78&userType=2&paralmported=null&orgNplId=null&showParaLink=null&hasEnvSection=yes&paraInfo=null&orgCompany=null&docId=IDE4POIFUCEQ5VERT1_IDX0000000174&fontSize=standard

Table 23: examples of procedural aspects for a non-exhaustive list of medicines containing Fluorouracil

Actikerall® 5 mg/g + 100 mg/g	Decentralised procedure RMS: Germany CMS: Austria, Czech Republic, Luxembourg, Poland, Slovak Republic, United Kingdom	No information available	No information available	No information available	No information available on EPAR: mri.medagencies.org/Human/Product/Details/19902

Fluorouracil® 50mg/ml Solution for Injection or Infusion	The application was submitted in 2009, through a decentralised procedure. RMS: UK CMS: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Slovakia, Spain and Sweden	The application was submitted in 2009, as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Fluorouracil 50mg/ml Injection which was authorised the 4th January 1996 to Mayne Pharma (MAH). The end of procedure was on the 28th April 2009 and the MA was granted on the 10th June, 2009	No mention of ERA nor environmental considerations	No information available	PAR coming from the RMS UK. www.mhra.gov.uk/home/groups/par/documents/websiteresources/con051925.pdf
Xeloda®, film-coated oral tablets in 150 or 500 mg, containing Capecitabin, pro-drug of 5-Fluorouracil Capecitabin Accord® – Generic of weloda®	Decentralised procedure in 2001 Authorisations have been awarded to Glenmark, AstraZeneca, Actavis and AET for both the 150 and 500 mg dosage strengths. RMS: UK Centralised procedure in 2012, under Article 3 (3) of Regulation (EC) No.	Xeloda was granted authorisation in EU in February 2001 for first line monotherapy of patients with metastatic colorectal cancer. The indication was subsequently extended through a Type II variation.	In the EPAR published by the UK, the only mention made to possible environmental effects relates to Capecitabine and states: "Exposure to the environment of Capecitabine, pro-drug of 5-Fluorouracil, is considered very limited and therefore no risk of concern would be expected" An ERA was published by the FASS in Sweden, based on	No	Scientific discussion for the MA of Xeloda available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000316/human_med_001157.jsp&mid=WC0b01ac058001d124 www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000316/WC500058145.pdf Information related to ERA available

726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 September 2010.

Swedish use and concentrations.

In the case of Capecitabin Accord, "No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Capecitabine Accord manufactured by Accord Healthcare Ltd is considered unlikely to result in any significant increase in the combined sales volumes for all capecitabine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased".

at: http://www.fass.se/pdfprint/servlet/se.lif.fass.pdfprint.servlets.ConvertServlet?nplId=20010202000030&docTypeId=78&userType=2&paraImported=null&orgNplId=null&showParaLink=null&hasEnvSection=yes&paraInfo=null&orgCompany=null&docId=IDE4POIFUCEQ5VERT1_IDX0000000174&fontSize=standard

EPAR for Capecitabin Accord: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002386/WC500126899.pdf

Fluoxetine

Active substance and product information

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRi) class. It is contained in several products such as[382]:

- Fluoxetine Actavis® 20 mg capsule
- Fluoxetine Alter® 20mg orally disintegrating tablets
- Fluoxetine EG® 20mg orally disintegrating tablets:
- Fluoxetine Sandoz® 20 mg capsule
- Prozac® 20mg capsule
- Fluoxetine TEVA® 20 mg capsule
- Symbyax®(Fluoxetine in combination with olanzapine) capsule: 5 dosages, measured in mg olanzapine/mg Fluoxetine: 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg.
- Sarafem® 10 -15 or 20 mg tablets
- Fontex® 20 mg capsule
-

Fluoxetine is used worldwide for the treatment of major depression (including paediatric depression), obsessive-compulsive disorder (in both adult and paediatric populations), bulimia nervosa, panic disorder and premenstrual dysphoric disorder. In addition, Fluoxetine is used to treat trichotillomania if cognitive behaviour therapy is unsuccessful. The common dosage of Fluoxetine for adult is 20 mg/day but can be prescribed up to 60 mg/day. The mean duration of the treatment is between 6 months and one year. Despite the availability of newer agents, Fluoxetine has remained extremely popular since 1988. In 2010, over 24.4 million prescriptions for generic formulations of Fluoxetine (it went off patent in 2001) were filled in the US alone (Verispan, 2011). In 2011, 6 million prescriptions for Fluoxetine were handed out in the UK[383] and 23.1 million Defined Daily Doses were prescribed in 2003 in Germany, reflecting a total amount of 4.62 tons of active substance (Schwabe, 2004). During the 2001-2009 periods, it was prescribed to more than 34 million people over the world (Demeestere, 2010) (Schultz, 2010).
Corresponding medicinal products are only delivered under prescription.
In 2012, researchers discovered that Fluoxetine has the potential to act as an antiviral in the treatment against enteroviruses such as polio (Sandle, 2012), which was a major breakthrough as there are no medicinal products currently in existence that can be used in the treatment of these viruses.

382 List of all products at : www.doctissimo.fr/principe-actif-5421-FLUOXETINE.htm
383 Patrisha Macnair (September 2012). "BBC - Health: Prozac"

Fluoxetine also can be used as a veterinary medicinal product. Reconcile is an antidepressant tablet for dogs, with a posology of 1-2 mg/kg (8, 16, 32 or 64 mg/pill dosage)[384].

Scientific information

Environmental aspects

Contamination pathway and behaviour in environment

Fluoxetine is metabolised and excreted mainly via urines and faeces (despite approximately one tenth of the adult therapeutic dose of Fluoxetine is excreted in breast milk (Taddio, 1996)). Up to 11% of the product is excreted via urine as non-metabolised Fluoxetine (Morando, 2009). The metabolisation products are Fluoxetine glucuronide, Norfluoxetine glucuronide, and Hippuric acid. Norfluoxetine is the only biologically active metabolite of Fluoxetine and is also a selective serotonin reuptake inhibitor. 80% of an oral dose of Fluoxetine is excreted in urines (11.6% unchanged (Fluoxetine), and 88.4% of metabolised products , including 7.4% of Fluoxetine glucuronide, 6.8% of Norfluoxetine, 8.2% of Norfluoxetine glucuronide, > 20% of Hippuric acid, and of 46% other uncharacterised compounds) and 15% is excreted in faeces[385] (Stein, 2007) (Vaswani, 2003).

The bioavailability of Fluoxetine and Norfluoxetine is relatively high (72%) but their excretion rates are extremely slow, which distinguish them from others antidepressants. With time, Fluoxetine and Norfluoxetine inhibit their own metabolism (especially many isozymes of the cytochrome P450 system essential for drug metabolism), so Fluoxetine elimination half-life changes from 1 to 3 days, after a single dose, to 4 to 6 days, after long-term use[386] (Burke, 2000). Similarly, the elimination half-life of Norfluoxetine is longer: about 9 days for a single dose, and up to 16 days after long-term use (Hiemke, 2000). Likewise, complete excretion of the medicinal product may take several weeks. The metabolisation rate is the same for humans and dogs.

As a result, the main contamination pathways from these oral antidepressants are so the discharge in wastewaters and sewage network of urines containing both their active pharmaceutical ingredient Fluoxetine and its metabolites. At least circa 4.0 micrograms of biologically active Fluoxetine and Norfluoxetine are released per treated adult every day in sewage waters (based on a 20 mg/day Fluoxetine dosage). The total quantity of Fluoxetine released each year around the world in sewage waters yields between 400 and 800 g. Nevertheless, the removal efficiency of the wastewater treatment plants is not high because treatments are not optimised for pharmaceutical products (only 30-70% of Fluoxetine can be removed with those treatments and more than 100 ng/L of Fluoxetine were detected in WWTP effluents (AMPERES, 2009)). As a result, the remaining active substances and/or its conjugate contained in treated wastewater or sludge are released into the natural environment (Schultz, 2010).Sewage sludge amendment of soils is also a route of environmental contamination by Fluoxetine, which was demonstrated to have a low biodegradability (Redshaw, 2008).

384 www.cbip-vet.be/fr/texts/FZSOOOL1EL20.php
385 www.healthystock.net/drugs/prozac.shtml
386 Prozac Pharmacology, Pharmacokinetics, Studies, Metabolism". RxList.com. 2007. Retrieved April 14, 2007.

In addition, wastewater from medicinal products production can also potentially be a source of Fluoxetine release in the environment (Fick, 2009).

▷ Exposure

In order to perform ecological risk assessment a review study roughly estimated Fluoxetine EICs (Environmental Introduction Concentrations) in the United States using annual consumption data for the year 2000 (Brooks, 2003). The PEC (Predicted Environmental Concentration) for Fluoxetine is approximately 0.439 µg/L if instream dilution, degradation, and metabolism are not included in these estimations, similar with another PEC of 0.37 µg/L estimated for the UK (Webb, 2001). When norfloxetine metabolite is included in PEC calculations, a value of 44 ng/L was calculated for systems not receiving dilution. Further, a PEC of 4.4 ng/L was generated when metabolism and a 10-fold dilution factor (which take into account the dilution of WWTP effluents in surface waters) were considered, similar to another reported PEC of 3 ng/L which included WWTP biodegradation and 10-fold dilution factors.

As a confirmation to the calculations, several investigators detected Fluoxetine in surface waters and municipal effluents (Silva, 2012), which establishes the environmental exposure to Fluoxetine, contrary to norFluoxetine which has not been detected yet in the environment. The Fluoxetine concentration in surface water was reported at 12 ng/L in US streams (Kolpin, 2002) but measured up to 54 ng/L in sewage treatment plants (Weston, 2001) or at 1 µg/L in Canadian WWTP effluent (Metcalfe, 2003). In Europe, the concentration of Fluoxetine in a Spanish river was measured at 21.4 ± 31.2 ng/L (Fernández, 2010) with a great variation between seasons due to rainfalls and WWTPs overflowing. An up-to-date systematic review (Hughes, 2013) of all data available on Fluoxetine detection in the environment conclude that its median concentration is about 18 ng/L (based on 12 studies) but this molecule can be detected at a concentration up to 600 ng/L.

A Norwegian study assessed that hospitals are not an important source of Fluoxetine in the environment as they monitored between 0.0 and 3.0 ng/L in hospital effluents (Langford, 2009).

▷ Impacts

Because of its serotonergic action, Fluoxetine was shown to influence the reproductive behaviour of molluscs (Hecker, 2004). Exogenous application of serotonin as well as Fluoxetine to *Dreissena polymorpha* induced spawning (Fong, 1998). The lowest observed effect concentration (LOEC) of 0.155 mg Fluoxetine/L for male mussels and 1.55 mg/L for female mussels has been reported. The reproduction is also reduced in other aquatic invertebrates: in the freshwater mudsnail *Potamopyrgus antipodarum*, the No Observed Effect Concentration (NOEC) and 10% Effect Concentration (EC10) were determined to be 0.47 and 0.81 µg/L respectively (Nentwig, 2007). Observations of Japanese medaka fish (*Oryzias latipes*) embryos indicated that developmental abnormalities were 4- 5 times more frequent when the fish was subjected to Fluoxetine (Foran, 2003). The lowest observed response level of Fluoxetine on aquatic biota occurs at concentrations detected in municipal effluents and at one order of magnitude higher than highest surface water concentrations reported.

Several EC50 (50% Effect Concentration) data are available for microorganisms, protozoa, algaes and fishes in bioassays studies. An EC50 for *Pseudokirchneriella subcapitata* growth was

estimated at 24 mg/L(Bruce, 1992). Average LC50s (50% Lethal Concentration) for *Ceriodaphnia dubia*, *Daphnia magna* and the fish *Pimephales promelas* were 234, 820, and 705 mg/L, respectively (Brooks, 2003).

The toxicity of Fluoxetine can vary following the isomer. After 24h incubation, the protozoa *Tetrahymena thermophila* EC50 is about 30 mg/L for (R) isomer of fluoxetin and only 3.2 mg/L for the (S) isomer, which is much more toxic (Andre, 2009).

Fluoxetine has been shown to have antimicrobial activity mainly against Gram-positive microorganisms. It also shows synergistic activity when combined with some antibiotics against several bacteria (Munoz-Bellido, 2000). It can also potentially exert its toxicity by inhibiting cellular efflux pumps (Munoz-Bellido, 2000).

In 2010, the EU-funded Environmental Risk Assessment of Medicinal products (ERAPharm) project has selected Fluoxetine to perform an environmental risk assessment (Oakes, 2010) due to its environmental persistence, acute toxicity to non-target organisms and unique pharmacokinetics associated with a readily ionisable compound. In Phase I of the assessment, the initial predicted environmental concentration of Fluoxetine in surface water reached or exceeded the action limit of 10 ng/L (set by the EMEA European guideline in 2006) when using both a default market penetration factor and prescription data for Sweden, Germany, and the United Kingdom. The Phase II of the risk assessment identified green algae as the most sensitive species with a NOEC of <0.6 µg/L. From this value, a predicted no effect concentration for surface waters of 12 ng/L was derived. The PEC/PNEC ratio was above the trigger value of 1.0 in worst-case exposure scenarios indicating a potential risk to the aquatic compartment. In addition, risks of Fluoxetine for sediment-dwelling organisms could not be excluded. No risk assessment was conducted for the terrestrial compartment due to a lack of data on effects of Fluoxetine on soil organisms.

- **Human health**

The potential effects of Fluoxetine residues in the environment on the human health are still unknown. A Dutch study (de Jongh, 2012) assessed the toxicological relevance for human health of the Fluoxetine and its parent compounds found in surface waters, treated surface waters and drinking waters by calculating a drinking water provisional guideline value and comparing maximum concentration levels present in the samples with this guideline value. They did not detect Fluoxetine in drinking water, contrary to the British authorities. They conclude that no adverse health effects of Fluoxetine detected in the sources of drinking water are expected in the Netherlands.

Procedural aspects, ERA and risk mitigation options

The first medicinal product containing Fluoxetine authorised in the market was the product PROZAC capsules, which was authorised in 1988 through a European centralised procedure without the necessity to perform an ERA. The authorisation of the next hybrid forms of this product (such as PROZAC liquid for example) only required abridged centralised procedures. However, the ERA performed on the product RECONCILE (similar to PROZAC) concluded that it was environmentally safe.

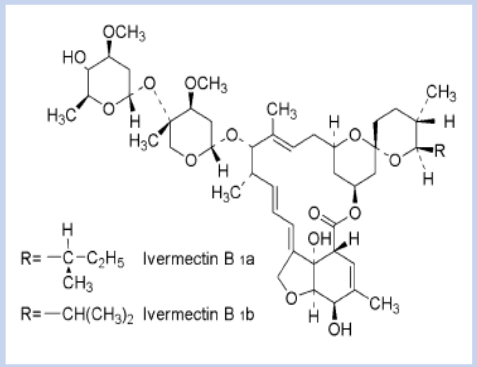
Most products placed on the market are generics (not mentioned in the following table), derived from long-term commercialised medicines. The majority of products have followed a decentralised procedure, which allows these products to be extensively placed on the market in the EU. In this case, marketing authorisation (MA) is granted without ERAs, with sometimes the commitment of MA holders to perform ERA *a posteriori*. In this case, ERA dossiers could not be retrieved on the relevant websites.

Ivermectin

Active substance and product information

Ivermectin is a broad-spectrum anti parasitic agent for both human and veterinary uses. It is the most used avermectin, which are macrocyclic lactons isolated from the soil actinomycete *Streptomyces avermitilis.* They are an important group of VMPs in terms of both their widespread use and their potential environmental risks (Campbell, 1983). They have been used in agriculture and horticulture for the protection of fruits, cotton, vegetables, and ornamentals (Dybas, 1989), because they are effective against a wide range of nematodes, mites, and insects (Omura, 2008).

Ivermectin consists of 80% 22,23-dihydroavermectin (B1a) and 20% 22,23-dihydroavermectin (B1b); (Figure 1), a synthetic derivative of the naturally occurring avermectin B1. Ivermectin binds selectively and with high affinity to the ligand glutamate on the ligand-gated chloride ion channels that occur in invertebrate nerve and muscle cells, causing irreversible opening of these channels (Rohrer, 1995). Furthermore, Ivermectin affects g-aminobutyric acid (GABA)-related chloride ion channels occurring in the peripheral nervous system of invertebrates and in the central nervous system of vertebrates (Duce, 1985). From a food safety perspective, the margin of safety for Ivermectin is attributable to the facts that 1) mammals do not have glutamate-gated chloride channels, and 2) the macrocyclic lactons have a low affinity for other mammalian ligand-gated chloride channels and do not readily cross the blood–brain barrier (Boelsterli, 2003).



parameter	value	parameter	value
Molecular mass	874.7	Henry constant	4.8×10^{-26} (est)
pKa	Neutral at all pH values	Water solubility (mg/L)	4.0 (m), 4.1 (m), 2.0 (m)
Melting point (°C)	349.8 (est)	Log K_{ow}	3.2 (m)
Vapor pressure (Pa)	$<1.5 \times 10^{-9}$ (m)	Log K_{oc}	3.6-4.4 (m)

Figure 14 : (left) Chemical structure of Ivermectin; (right) physicochemical properties of Ivermectin, adapted from (Liebig, 2010).

The most extensive use of avermectins is in the control of livestock parasites. Ivermectin also has been used in veterinary medicine since 1981. It sometimes is administered in combination with other medications to treat a broad spectrum of animal parasites (Canga, 2009). It is used regularly as a parasiticide for cattle, pigs, sheep, horses, and dogs (Forbes, 1993). Its most

common form is a solution for injection with 10 mg/mL Ivermectin. It is one of the most widely used medications in preventing heartworm infection in dogs. It also is used in cats for the same purpose but to a lesser extent. For example, the Acarexx 0.01% Ivermectin topical preparation is prescribed for treating ear mites in cats. Some of the most well known of the brands of heartworm prevention medications that contain Ivermectin include Heartgard Plus®, Iverhart Plus®, Iverhart Max® and Tri-Heart®.

Ivermectin also is used worldwide as human medicine against worm infestations. It is, for example, primarily used in the treatment of Onchocercisis (river blindness), Strongyloidiasis (diarrhea), Ascariasis or Filariasis; and it is also effective against some epidermal parasitic skin diseases, including scabies and lice. For example, Ivermectin 0.5% lotion is able to eradicate lice from 80% patients after two weeks using a single application.

Ivermectin kills by interfering with nervous system and muscle function, in particular by enhancing inhibitory neurotransmission. In worms, it appears to work by paralyzing and then killing the offspring (microfilaria) of adult worms. It may also slow down the rate at which adult worms reproduce. It is contained in several products such as[387]:

- Human medication :
  - Mectizan 3 mg Ivermectin tablets
  - Stromectol 3 mg Ivermectin tablets
- Veterinary medication :
  - Heartgard Plus tablets (Ivermectin in combination with pyrantel pamoate, ratio 136 µg Ivermectin/114mg pyrantel)
  - Ivomec 3 mg ivermectin tablets
  - Acarexx : 0.01% Ivermectin liquid preparation
  - Divamectin 1% solution for injection (10 mg/mL)
  - Vetermec injectable solution (10 mg/mL)
  - Closiver solution for injection for sheep (Ivermectin in combination with closantel, ratio 5 mg/mL Ivermectin/ 125 mg/mL closantel)
  - Closiver solution for injection for cattle (Ivermectin in combination with closantel, ratio 5 mg/mL Ivermectin/ 200 mg/mL closantel)
  - Iveryin cattle: Generic
  - Ivermectin Vibrac Vet
  - Virbalan Vet (Eraquel Equimel): Generic

The common dosage of Ivermectin for adults is 150-200µg/kg body weight, representing approximately a dosage of 15 mg/adult. This dosage must be taken once annually to be effective,

387 List of veterinary products at : http://ec.europa.eu/health/documents/community register/2009/2009100169288/anx_69288_en.pdf

and the treatment continues throughout one's lifespan. Ivermectin is used in animals in many dosage ranges, depending on the purpose of its usage (for example 200-300µg/kg body weight for cattle, sheep and pig). Dosages used for preventing heartworm infections are generally relatively low, with low risk of side effects. Higher dosages, such as those used to treat demodectic mange, sarcoptic mange, ear mites and other parasitic infections, are more likely to be associated with adverse reactions. Corresponding medicinal products are only delivered under prescription.

The global antiparasitic veterinary market represents 28% of the global European veterinary medicine market (4.3 billion Euros in 2010) and is equivalent to 1.2 billion Euros, including 0.3 billion Euros in France[388]. On the contrary, antiparasitic is the smallest therapeutic class in the European human market, as it represents only 0.3% of the global French medicine market (ANSM, 2012) in terms of both sold quantities and revenues.

Since 1981 and its introduction in the veterinary market, Ivermectin quickly has become a remarkable success, rapidly capturing a large portion of the global veterinary antiparasitic market. It became the market leader within two years, and it has maintained that position ever since with annual sales of about U.S $1 billion. Since its market introduction in the early 1980s Ivermectin with over 5 billion doses sold worldwide, has become the most widely used antiparasitic medicinal product (Shoop, 2002). Since the introduction of Ivermectin, several other endectocides have appeared, but none has replaced Ivermectin as the market leader (Omura, 2004). Five years after its introduction, Ivermectin was registered for use in 46 countries and was being used worldwide to treat approximately 320 million cattle, 151 million sheep, 21 million horses and 5.7 million pigs.

In human health, Ivermectin is extensively used in tier world (30 African countries, six Latin American countries, and Yemen) for mass treatment against Onchocercisis: between 65 and 80% of the population is treated once a year with a 150 µg/kg dosage at least for 30 years (Winnen, 2002). In 2003, approximately 56 million Africans were taking a single annual dose of Ivermectin[389].

Environmental aspects

▷ Contamination pathway and behaviour in environment

The main route of excretion is via faeces (Chiu, 1986), which provides a microhabitat and breeding ground for a very large number of invertebrate species, on which avermectins are known to have deleterious effects. Ivermectin is metabolised in the liver and Ivermectin and/or its metabolites are excreted almost exclusively in the faeces (90%) over an estimated 12 days for humans and between 10 and 150 days for animals, with less than 1-2% of the administered dose excreted in the urine[390]. Ivermectin is also excreted in milk (Alvinerie, 1997). Ivermectin undergoes little metabolism; most of the dose is excreted unchanged, nevertheless, some metabolites can also be detected in faeces, but their nature is different depending on the

388 www.merci-les-medicaments-veterinaires.com/enjeux.php?id_menu=56.
389 Mectizan Donation Programme. (2004) Newsletter of the Mectizan Donation Programme at www.mectizan.org/mpn33/mpnhtml336.htm
390 www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf

organism (Canga, 2009).In animals, the excretion profile of Ivermectin in faeces reveals that 70% of a dose is excreted, 90% of which is excreted in 4 days in faeces (Perez, 2001). The peak concentration is obtained between 2 and 6 days after injection and varies between 0.36 and 2.5 mg/kg (Cook, 1996), but the molecule remains detectable above 0.5 µg/kg up to 40 days after injection. Oral applications tend to result in sharp excretion peaks with most of the dose excreted over a few days as metabolites. Peak elimination of injectable or topical formulations usually occurs within 2 to 7 days post treatment followed by a long tail that may last for more than 4 to 6 weeks, whereas peak elimination levels of sustained-release formulations may occur over several weeks post treatment (Floate, 2005).

As a result, Ivermectin and its metabolites contained in veterinary medicines can reach terrestrial and aquatic ecosystems by two main routes: direct dung deposition by pasture animals or manure application on agricultural lands (Kövecses, 2005). Moreover, Ivermectin and its metabolites contained in human medicine can reach terrestrial and aquatic ecosystems by one main route: sewage sludge amendment of agricultural lands.

▷ **Environmental fate**

Abiotic fate

Ivermectin is hydrolytically unstable both in acidic and in basic solution, being most stable at a pH of 6.3 (Fink, 1988). Data on hydrolysis in environmental matrices were not Ivermectin determined in a thin, dry film exposed to direct sunlight for approximately 3h (Halley, 1989). Photo-induced reactions are thus anticipated to influence the fate of Ivermectin in the aquatic environment. Results of a long-term outdoor aquatic mesocosm study (Sanderson, 2007) with Ivermectin using natural water and sediment suggest that both processes play a minor role, insofar as Ivermectin dissipates rapidly from the water phase into the sediment.

Sorption

Table 7 shows results for studied sorption of Ivermectin in a clay loam and a silty loam soil. Equilibrium distribution was reached within 48 h and 16 h respectively (Krogh, 2008). The estimated Kd values (average values of sorption and 2 desorption steps) from the latter experiments were 227 and 333 L/kg, corresponding to log KOC values of 3.6 to 4.4, indicating strong sorption (Liebig, 2010). In soil column experiments with two soils containing 2.3 and 6.3% organic carbon content, no Ivermectin was detected in the leachate (Oppel, 2004), whereas in another study, 27% to 48% of the applied 3H radioactivity was leached as transformation products, and 39% to 49% remained in the top 5 cm of the soil column. The identity of the strongly sorbed fraction remained undetermined but was assumed to be mostly the parent substance. The limited mobility of Ivermectin in soils justifies the assumption of little potential for groundwater contamination.

Table 24: Soil parameters, sorption/desorption properties and organic carbon normalised adsorption coefficients of Ivermectin for five different soils, adapted from (Liebig, 2010).

artificial	6.0	0.047	0.0273	109	141-246	4.00×10^3	3.6
York, UK	6.3	0.0265	0.0154	396	54-201	2.58×10^4	4.4
Madrid, E	8.7	0.0077	0.0045	57	28-56	1.28×10^4	4.1
Newton, US	5.5	0.039	0.0226	333	Not determined	1.47×10^4	4.2
Fulton, US	6.3	0.025	0.0145	227	Not determined	1.57×10^4	4.2

Degradation and Transformation in soil

Transformation of Ivermectin in soil indicates that dissipation half-lives (DT50) in soil can be rather variable depending on soil type, sorption capacity, temperature, and oxygen availability (Liebig, 2010). The highest DT50 of 67 d was derived with a simple first-order model for natural soil at 20 °C under aerobic conditions. This DT50 was used as a worst-case value in the exposure assessment. Within the study of Krogh et al. (2008), 2 transformation products of Ivermectin were identified in soil, a monosaccharide and an aglycone of Ivermectin (22,23-dihydroavermectin B1 monosaccharide and 22,23-dihydroavermectin B1 aglycone).

Degradation in manure water–sediment systems

Reports of low Ivermectin persistence in manure following summer or dry conditions is observed but might be an artefact resulting from reduced Ivermectin extraction efficiency at low moisture content of the solid matrix (Pope, 2010). Degradation of Ivermectin in water–sediment systems was investigated using natural sediment containing 4.5% total organic carbon (TOC), with resulting compartment-specific degradation half-lives (t1/2) and an estimated dissipation half-life (DT50) in water of <0.25 d (Prasse, 2009). Løffler et al. (2005) also investigated the fate of Ivermectin in water–sediment systems. The authors found a dissipation half-life (DT50) of 15 d for the whole system containing natural sediment.

▷ Exposure

Several studies have addressed the exposure and effects of Ivermectin in the environment (Floate, 2005), but few studies have been carried out according to standardised guidelines.

Non-target soil organisms can be exposed to Ivermectin via faeces, sprayed manure of Ivermectin-treated animals or sewage sludge used in fields that contain large quantities of Ivermectin excreted by animals and humans (up to 80–90% (Alvinerie, 1999)). Ivermectin concentrations in freshly excreted dung ranging from 0.31 to 0.81mg /kg (dung dry weight (dry wt)) lead to soil concentrations (uppermost soil layer) of up to 0.085 mg of Ivermectin by kg of soil (dry wt) (Römbke, 2010). Another study presented estimates of 0.2 ppb the environmental

load of Ivermectin due to the manure release of one herd (Bralet, 2002), equivalent to 0.016 mg/m².

In contrast, aquatic non-target organisms are rather exposed indirectly, through runoff incidents or transport of eroded soil from pasture and arable land, with the exceptions of direct Ivermectin use in aquacultures (Collier, 1998) or the possibility that treated animals excrete directly into water (Boxall, 2004). A semi-field study (Fernadez, 2011) was conducted to assess the Ivermectin dynamic in runoff and drainage waters from dung-treated soils. Ivermectin was only detected in the drainage and runoff waters collected in the first rainfall events after treatment. The measured concentrations in drainage water varies between 0.006 and 0.118 ng/ml and runoff particles are in the range of 0.052–5.89 ng/mg dry suspended matter. Nevertheless, due to a K_{OC} of 1172 L/kg and a low water solubility (intrinsic solubility: 2mg L^{-1}(Escher, 2008)), Ivermectin partitions rapidly from the water phase to sediment particles (Løffler, 2005) so low Ivermectin concentrations remain in surface waters.

In order to perform an ecological risk assessment, a review study roughly estimated Ivermectin PECs (Predicted Environmental Concentrations) in sediments (Liebig, 2010) based on the 2008 EMEA European guidelines. For pasture animals directly excreting into surface water, the $PEC_{Sediment}$ values were 0.83 and 2.17 µg/kg (dry wt) for best and worst case scenarios, respectively. The $PEC_{Sediment}$ values anticipated in intensively reared animal scenarios were 0.45 and 0.65 µg/kg dw (best and worst case).

A study (Slootweg, 2010) assessed the bioaccumulation of Ivermectin from sediments in the benthic organism *Lumbriculus variegates* and concluded, based on bioaccumulation factors ranging from 0.2 to 11.0, that Ivermectin has a great potential to bioaccumulate, indicating a risk for biomagnification of the compound in the food chain.

▷ **Impacts**

Thanks to a large amount of ecotoxicological study, it is now well established that Ivermectin is highly toxic to several non-target organisms. A high toxicity was found for nonparasitic invertebrates (Edwards, 2001). The first study raising environmental concern was conducting in 1989 (Halley, 1989) and was successively corroborated by newer studies.

Aquatic short-term effect studies

Ivermectin has been found to be extremely toxic to aquatic crustaceans, in the nanogram per litre range (Garric, 2007). The highly toxic effects on the free-living nematode *Caenorhabditis elegans* (Ardelli, 2009), the oligochaete *Lumbriculus variegates* and the midge *Chironomus riparius* (Egeler, 2010), and pulmonate snails (Okafor, 1990) were demonstrated. Cladocerans (e.g., *Daphnia magna, Ceriodaphnia dubia*) have been shown to be extremely sensitive to Ivermectin, even at concentrations as low as 0.001–25 ng/L (Halley, 1989).

Due to a rapid sorption to sediment particles and high persistence in aquatic sediments, Ivermectin is also toxic for benthic organisms. Benthic microcrustaceans (cladocerans, ostracods) and nematodes showed the most sensitive response to Ivermectin, while tardigrades profited from the presence of the pharmaceutical. The $NOEC_{Community}$ values for meiofauna and nematode communities are respectively 6.2 and 0.6µgk/g dw (Brinke, 2010) . Those values are close to the estimated PECs in sediments (0.45–2.17µg/kg dw, see "exposure" section), resulting in RQs

between 1.05 and 36.2. This indicates that the effects of Ivermectin on meiobenthic organisms are likely to occur in freshwater ecosystems. Likewise, the measured concentrations in drainage water of dung-treated soils (see semi field study in previous "exposure" section) are orders of magnitude higher than those provoking effects on aquatic and benthonic communities under experimental and mesocosm conditions.

In 2010, the EU-funded Environmental Risk Assessment of Medicinal products (ERAPharm) project has selected Ivermectin to perform an environmental risk assessment (Liebig, 2010) due to its environmental persistence, accumulation in soils and acute toxicity to non-target organisms. For the environmental compartments surface water, sediment, and dung, this ERA revealed a risk at all levels of the tiered assessment approach, contrary to other previous ERAs which had concluded that there was no concern for the aquatic compartment. Only for soil was no risk indicated after the lower tier assessment. The main results of this study are summed up in the following section.

The base set data according to EMA on short-term effects to fish, *Daphnia*, and algae from the literature is supplemented in Table 25. A growth-inhibition test with the green alga *P. subcapitata* exposed to Ivermectin performed according to OECD 201 yield a EC50>4.0mg/L. Ten Daphnia immobilisation tests were performed according to OECD 202. To avoid photodegradation, these tests were conducted in the dark. EC50 values ranged from 1.2 to 10.7 ng/L (mean value 5.7 ng/L). These values are slightly below the LC50 of 25 ng/L derived for *D. magna* for another study. These data shows that Ivermectines are extremely toxic to *Daphnia*.

The scientific literature shows that acute effect data of Ivermectin on fish occurs in the lower micrograms- per-liter range, with *Oncorhynchus mykiss* as the most sensitive species. Overall, crustaceans are the most sensitive taxonomic group, showing effect concentrations in the lowernanograms-per-liter range.

Table 25: Aquatic short-term effect studies, adapted from (Liebig, 2010)

Pseudokirchneriella subcapitata **(green algae)**	OECD 201	$EC_{50\ 72h,\ yield,\ growth\ rate}$ > 4 mg/L $LOEC_{\ 72h,\ yield,\ growth\ rate}$ = 1.25 mg/L $NOEC_{\ 72h,\ yield,\ growth\ rate}$ = 391 µg/L	(Garric, 2007)
Daphnia magna **(crustacean)**	OECD 202	$EC_{50\ 48h,\ immobility}$ = 1.2-10.7 ng/L Mean $EC_{50\ 48h,\ immobility}$ = 5.7 ng/L	
	USEPA 660/3-75-009	$LC_{50\ 48h}$ = 25 ng/L	(Haley, 1989)
Oncorhynchus mykiss **(fish)**	USEPA 660/3-75-009	$LC_{50\ 96h}$ = 3.0 µg/L	
Salmo salar **(fish)**	Acute toxicity test (juvenile fish)	$LC_{50\ 96h}$ = 17 µg/L	(Kilmartin, 1996)

Terrestrial effect studies

Field studies have demonstrated that the dung of animals treated with Ivermectin supports a significantly reduced diversity of invertebrates, and that the dung persists longer (Iglesias, 2006). For example, a significant decrease in the abundance of adult dung beetles was observed at 0.81mg Ivermectin / kg of dung (dw) (Römbke, 2010). For the dung beetle species, *Volinus*

distinctus, a No Observed Effect Concentration (NOEC) and a median effect concentration (EC50) of 0.50 and 0.62mg / kg dung were respectively determined. Dung fly larvae were found to be the most sensitive dung fauna group as their abundance was significantly reduced in all Ivermectin treatments, resulting in a NOEC <0.31mg/kg.

The very negative impacts of the Ivermectin on fauna not-target (mites, dipterous and coleopters coprophages) were established by very many studies (a community-based NOEC was found below the lowest test concentration of 0.25 mg / kg (Jensen, 2012), whereas the EC10 for the individual species were as low as 0.05 / mg kg), even if the laboratory which markets it published some contradictory studies.

Results of the terrestrial tests are summarised in Table 26. Data on an earthworm reproduction test according to OECD 220/222 was found to yield an EC50 of 5.3 mg/kg dry wt and an NOEC of 2.5 mg/kg dry wt. The toxicity to non-target arthropods for parasiticides performed with collembolan reproduction according to ISO 11267 revealed a high sensitivity, as shown by the NOEC of 0.3 mg/kg dry wt. Earthworms and other oligochaetes were less sensitive, with NOECs in the milligrams-per-kilogram range. The high sensitivity of *Musca autumnalis* to Ivermectin was confirmed in a ring test performed to validate the OECD draft guideline, in which a mean EC50 of 4.65 mg/kg dung fresh wt was determined. In the literature, effect concentrations of 0.5mg/kg dung fresh wt were reported for the yellow dung fly *Scathophaga stercoraria* when studying morphological changes in adults. With LC50 values of 100 and 176mg/kg dung fresh wt, the dung beetle *Aphodius constans* reacted less sensitively to Ivermectin than dung flies. In a test with dung living nematode species, an NOEC of 3.0 mg/kg dung fresh wt was determined, which is higher than the values found for dung flies and beetles, although both insects and nematodes belong to the target organisms of Ivermectin.

Table 26: Terrestrial effect studies with soil and dung organisms, adapted from (Liebig, 2010)

Eisenia fetida **(earthworm)**	OECD 222	$NOEC_{28d, biomass}$ = 5.0 mg/kg dry wt $NOEC_{56d, reprod}$ = 2.5 mg/kg dry wt $EC_{50\ 56d, reprod}$ = 5.3 mg/kg dry wt	(Rombke, 2010)
	Subchronic earthworm toxicity test	$NOEC_{28d, biomass}$ = 12 mg/kg dry wt $LC_{50\ 28d}$ = 315 mg/kg dry wt	(Haley, 1989)
	OECD 207	$NOEC_{14d, biomass}$ = 4.0 mg/kg dry wt $LC_{50\ 14d}$ = 15.8 mg/kg dry wt	(Gunn, 1994)
Enchytraeus crypticus **(potworm)**	ISO 16387	$NOEC_{28d, reprod}$ = 3.0 mg/kg dry wt $EC_{50\ 28d, reprod}$ = 36 mg/kg dry wt $LC_{50\ 28d}$ > 300 mg/kg dry wt	(Jensen, 2003)
Folsomia fimetaria **(collembolan)**	ISO 11267	$NOEC_{28d, reprod}$ = 0.3 mg/kg dry wt $EC_{50\ 28d, reprod}$ = 1.7 mg/kg dry wt $LC_{50\ 28d}$ = 8.4 mg/kg dry wt	
Folsomia candida **(collembolan)**	ISO 11267	$NOEC_{28d, reprod}$ = 0.3 mg/kg dry wt $EC_{50\ 28d, reprod}$ = 1.7 mg/kg dry wt	(Rombke, 2010)
Musca autumnalis **(dung fly)**	OECD	$EC_{50\ 21d, emergence\ rate}$ = 4.65 µg/kg dung fresh wt	
Scathophaga stercoraria **(dung fly)**	OECD	$LC_{50\ 28d}$ = 20.9 µg/kg dung fresh wt $NOEC_{28d, development\ time}$ = 0.84 µg/kg dry wt	(Rombke, 2009)
	Specific test design (acute toxicity)	$LC_{50\ 48h, larvae}$ = 36 µg/kg dung fresh wt $EC_{50\ 3\text{-}4\ w, emergence}$ = 1.0 µg/kg dung fresh wt	(Strong, 1993)
Aphodius constans **(dung beetle)**	OECD draft	$LC_{50\ 21d}$ = 176 µg/kg dung fresh wt $LC_{50\ 21d}$ = 880 µg/kg dung dry wt $NOEC_{21d, larval\ survival}$ = 320 µg/kg dry wt	(Hempel, 2006)
		$LC_{50\ 21d}$ = 100 µg/kg dung fresh wt $LC_{50\ 21d}$ = 590 µg/kg dung dry wt	(Lumaret, 2007)

- **Human health**

The potential effects of Ivermectin residues in the environment on the human health are still unknown. However, its high potential of bioaccumulation and bioamplification along the food chain can raise some concerns about human contamination by environmental Ivermectin. According to VMD, 10% of salmon flesh samples from aquaculture contained residues of Ivermectin (Humphrys, 2001), which can represent a risk for young humans. Moreover, the risk for ingestion of Ivermectin though cow milk cannot be excluded even if it is illegal in animals that produce milk for human consumption (Alvinerie, 1997).

Procedural aspects, ERA and risk mitigation options

The first medicinal product containing Ivermectin authorised in the market was the product Ivermectin injection solution, which was authorised in 1981 in the UK through a national procedure with no reference to any ERA. National Marketing Authorisations for injectable products containing Ivermectin for use in cattle have been granted in all MS of the European

Union via different authorisation procedures (mutual recognition procedures or national procedures) and under various legal bases. Various procedures have been conducted: mainly because the procedures are product-based and not compound-based. Even as generic products, all these veterinary medicines needed an ERA before being marketed. The ERA was usually stopped at phase II. Environmental risks were considered acceptable if the products were used in conformity with rules (for example, limited access of treated cattle to aquatic sources).

IVOMEC for cattle and EQVALAN for horses	National procedures (UK)	Authorisation date: 30/09/1981	No reference to an ERA		
88 products veterinary products containing Ivermectin 10mg/mL	National procedures[391] (Autria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom)	Authorisation date: 28/10/2002 Authorisation renewal: 01/10/2009	Application for a generic product, according to Article 13 (1) of Directive 2001/82/EC with bioequivalent to the reference product: Ivomec Super Injection for Cattle (first authorised in UK in August 1987) so results of pharmacological and toxicological data were not required. The reference product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. The overall benefit/risk analysis is in favour of granting a marketing authorisation.		
Invertin Solution Injection for cattle	National and mutual recognition procedures[392] RMS : Spain CMS : Austria, Belgium, France, Germany, Italy and the United Kingdom	Authorisation date: 28/10/2002 Authorisation renewal: 01/10/2009	Application for a generic product, according to Article 13 (1) of Directive 2001/82/EC with bioequivalent to the reference product: Ivomec Super Injection for Cattle(first authorised in UK in August 1987) so results of pharmacological and toxicological data were not required. The reference	Suitable warning on SPC and product literature: highly toxic to aquatic invertebrates. Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment to avoid adverse effects on aquatic organisms.	PAR[393]

391 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:288:0011:0146:EN:PDF

392 National Marketing Authorisations for injectable products containing ivermectin for use in cattle have been granted in all the MS of the European Union via different authorisation procedures (mutual recognition procedures or national procedures) and under various legal bases. Various procedures have been held: mainly because the procedures are product based and not compound based.

393 www.vmd.defra.gov.uk/.../UKPAR_358881.doc

			product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. **The applicant provided first and second phase environmental risk assessments** in compliance with the relevant guideline. All PEC values were acceptable, but it was not possible to exclude a risk for aquatic organisms The overall benefit/risk analysis is in favour of granting a marketing authorisation.	Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.	
Closiver solution for injection for sheep	Mutual recognition (decentralised) procedure RMS : UK CMS : Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Italy, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden	Authorisation date: 10/05/2011	Yes, the ERA has been made and **has progressed to phase II** in compliance with the relevant guidelines. The risks were considered "acceptable and warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed"	Suitable warning on SPC and product literature: highly toxic to aquatic invertebrates. Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment to avoid adverse effects on aquatic organisms. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.	PAR[394]

394 www.vmd.defra.gov.uk/.../UKPAR_305902.doc

Ivermectin 'Vibrac' Vet	Mutual recognition procedure RMS: Denmark CMS: Belgium, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, United Kingdom	Authorisation date: 09/02/2006		
Eraquell Equimel Equimax 20 mg chewable tablets for horses	Decentralised procedure RMS: Denmark CMS: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden	Authorisation date: 29/04/2009	The applicant provided a **first phase environmental risk assessment** in compliance with the relevant guideline that showed that no further assessment was required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. The benefit/risk profile for the target species is favourable, and the quality and safety of the product for humans and the environment is acceptable.	PAR[395]

[395] www.imb.ie/images/uploaded/swedocuments/Eraquell%20Tabs%20Ivermectin%2020mg%20Chewable%20Tablets%20for%20Horses%20VPA%2010988-077-001.pdf

Ecomectin18.7mg/g Oral Paste for Horses	Mutual recognition procedure RMS : Ireland CMS : Denmark, Finland, Hungary, Portugal, Spain, Sweden	Authorisation date: 11/2007	An environmental risk was detected during the **risk assessment Phase II Tier A** for dung fauna organisms. No adequate data for Tier B was provided by the applicant to assess the long-term effects on dung fauna organisms caused by the use of the product. However, since the product is intended for use in a minor species (horses) that is reared and treated similarly to a major species, conclusions on the Environmental Risk Assessment of the major species apply, and the product should be exempt from providing a Phase II assessment and no risk mitigation measures should be included in the SPC of the product.	The ERA concluded that "No risk mitigation measures are considered appropriate".	PAR[396]
Bimectin Plus (Ivermectin + Clorsulon) (Generic)	Mutual recognition RMS : UK CMS: BE, DE, DK, ES, FR, IT, PL, PT, RO	Start of procedure (DayO) 23.09.2010 Final position 22.12.2010	Incomplete ERA due to outstanding studies and data. Phase II A performed, Phase II B missing Data published within the ERAPharm publication of e.g. Liebig et al. 2010 were taken into account for the assessment of ERA provided.	RMM imposed due to identified risk for the aquatic (Daphnia) and terrestrial (Dung organisms) compartment: The product is very toxic to aquatic organisms and dung insects. Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment. Long-term effects	General information available at EMA page for Ivermectin applications

[396] www.emea.europa.eu/docs/en_GB/document_library/Referrals_document/Ecomectin_33/WC500061770.pdf

on dung insects caused by continuous or repeated use cannot be excluded.
Repeat treatments on a pasture within a season should only be given on the advice of a veterinarian.
In accordance with VICH Phase II guidance RMM have to be imposed if a risk for the environment still exists at the end of *Phase II Tier B* "the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority". In this application the Phase II Tier B assessment could not be finalised. RMMs were imposed without the guideline conform finalisation of the Tier B assessment.

Tetracyclin

Active substance/product information

Tetracyclines belong to a subclass of polyketides that have a common octahydrotetracene-2-carboxamide skeleton (IUPAC, 1997). The group comprises the following antibiotics: Doxycycline, Chlortetracycline, Clomocycline, Demeclocycline, Lymecycline, Meclocycline, Metacycline, Minocycline, Oxytetracycline, Penimepicycline, Rolitetracycline, Tetracycline and Tigecycline (for human use only). Most tetracyclines belong to ATC Code J01A in the group J01 (antibacterials for systemic use). Some tetracyclines are however classified separately.

All tetracyclines share the same primary molecular mechanism of action, i.e. they bind to the procaryotic 30S ribosomal subunit and interfere with protein biosynthesis by inhibiting the binding of aminoacyl-tRNA to the mRNA-ribosome complex. The compounds are usually classified as bacteriostatic medicinal products, which do not kill bacteria but inhibit bacterial growth.

Scientific information

▶ Environmental aspects

▷ Exposure

Segura et al. (2009) published a summary of the available data from peer-reviewed studies on the concentrations of tetracyclines in wastewaters, natural waters, and drinking water (compiled in Table 27). No studies on concentrations of tetracyclines in drinking water were found. Data on Tetracycline, Chlortetracycline and Doxycycline and Oxytetracycline were most common ($n > 10$), while data on concentrations of Demeclocycline, Meclocycline, Minocycline were less common ($2 < n < 7$). Median concentrations in natural waters are typically in the range of tens to hundreds of ng/L, with maximum concentrations of up to 0.7 mg/L were found for Oxytetracycline. Median concentrations in wastewater are substantially higher and more diverse, with particularly high concentrations of Chlortetracycline (~0.08 mg/L) and Oxytetracycline (~1 mg/L). Maximum wastewater concentrations exceeding 1 mg/L were found for Chlortetracycline (12 mg/L), Oxytetracycline (920 mg/L), and Tetracycline (850 mg/L).

Table 27: Environmental concentrations of tetracyclines in natural waters and wastewaters (in ng/L, from (Segurra, 2009)

Compound	Matrix	Max	Median
Chlortetracycline	Wastewaters	12 000 000	80 450
Chlortetracycline	Natural waters	690	171
Demeclocycline	Wastewaters	3 150	1 140
Demeclocycline	Natural waters	440	185
Doxycycline	Wastewaters	6 700	83

Compound	Matrix	Max	Median
Doxycycline	Natural waters	73	30
Meclocycline	Wastewaters	1 070	435
Meclocycline	Natural waters	100	55
Minocycline	Wastewaters	8 900	4 640
Minocycline	Natural waters	n.d.	n.d.
Oxytetracycline	Wastewaters	920 000 000	1 100 000
Oxytetracycline	Natural waters	712 000	1 340
Tetracycline	Wastewaters	850 000 000	370
Tetracycline	Natural waters	110	560

n.d.: no publications on analytical findings could be identified by (Segurra, 2009).

Concentrations of tetracyclines in soil were identified from querying SCOPUS (Nov. 2012) and are compiled in Table 28. Only studies investigating Chlortetracycline (max. concentration ~1mg/kg, median 55µg/kg), Oxytetracycline (max. concentration ~5 mg/kg, median 0.1 mg/kg) and Tetracycline (max. concentration ~0.6 mg/kg, median 0.1 mg/kg) were found.

Peer-reviewed publications were identified from SCOPUS (Nov. 2012).

Table 28: Concentrations of Chlortetracycline, Oxytetracycline and Tetracycline in soil

chlortetracycline	30.0	(Sarmah, 2006)
chlortetracycline	39.0	(Sarmah, 2006)
chlortetracycline	93.0	(Sarmah, 2006)
chlortetracycline	41.8	(Boxall, 2003)
Chlortetracycline	7.0	(Hamscher, 2005)
Chlortetracycline	12.0	(Hamscher, 2005)
Chlortetracycline	39.0	(Hamscher, 2005)
Chlortetracycline	87.0	(Aust, 2008)
Chlortetracycline	55.0	(Aust, 2008)
Chlortetracycline	1079.0	(Hu, 2010)
Chlortetracycline	7.1	(Blackwell, 2005)

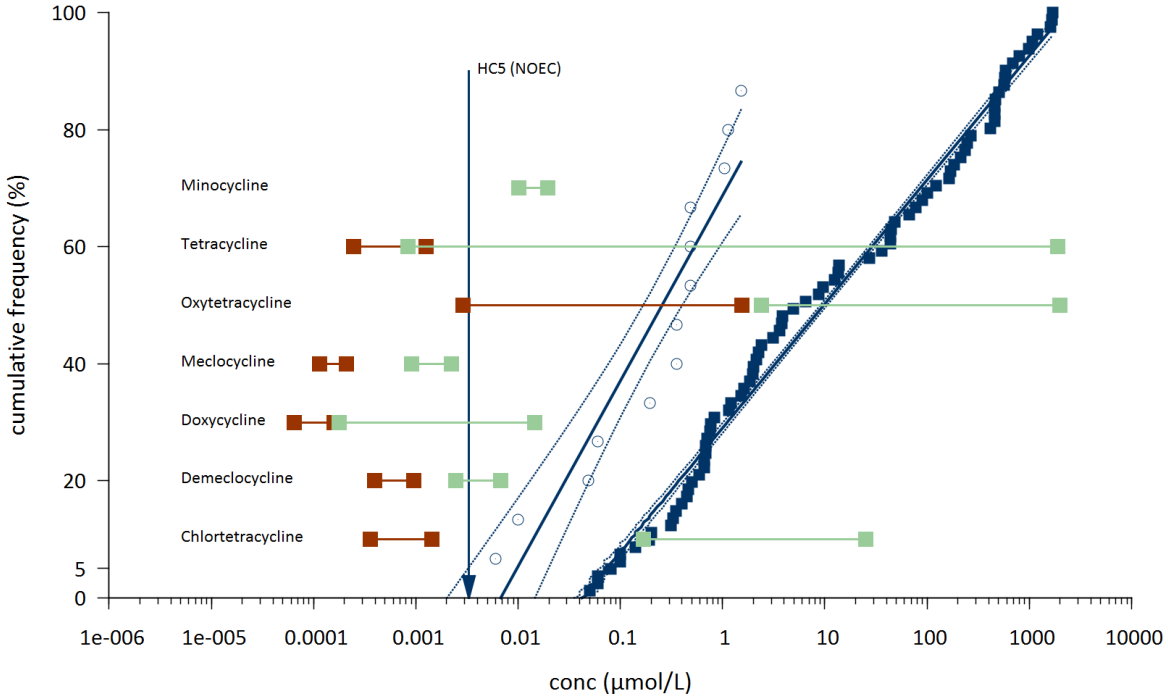
Chlortetracycline	6.0	(Blackwell, 2005)
Chlortetracycline	104.6	(Li, 2011)
Chlortetracycline	104.6	(Li, 2011)
Chlortetracycline	100.9	(Li, 2011)
Chlortetracycline	588.0	(Li, 2011)
Chlortetracycline	1079.0	(Li, 2011)
Chlortetracycline	0.9	(Ok, 2011)
Chlortetracycline	73.0	(Cengiz, 2010)
oxytetracycline	305.0	(Sarmah, 2006)
oxytetracycline	27.0	(Sarmah, 2006)
oxytetracycline	8.6	(Boxall, 2003)
Oxytetracycline	1691.0	(Kay, 2004)
Oxytetracycline	526.0	(Blackwell, 2007)
Oxytetracycline	148.0	(Blackwell, 2007)
Oxytetracycline	28.0	(Blackwell, 2007)
Oxytetracycline	24.0	(Blackwell, 2007)
Oxytetracycline	1000.0	(Kay, 2005)
Oxytetracycline	0.2	(Kay, 2005)
Oxytetracycline	2683.0	(Hu, 2010)
Oxytetracycline	7.0	(Blackwell, 2007)
oxytetracycline	25.0	(Watanabe, 2010)
Oxytetracycline	79.7	(Li, 2011)
Oxytetracycline	5172.0	(Li, 2011)
Oxytetracycline	2683.0	(Li, 2011)

Oxytetracycline	171.0	(Li, 2011)
Oxytetracycline	3.8	(Ok, 2011)
Oxytetracycline	105.0	(Cengiz, 2010)
Tetracycline	225.0	(Sarmah, 2006)
Tetracycline	295.0	(Sarmah, 2006)
Tetracycline	443.0	(Sarmah, 2006)
Tetracycline	12.0	(Jjemba, 2006)
Tetracycline	227.0	(Hamscher, 2005)
Tetracycline	295.0	(Hamscher, 2005)
Tetracycline	253.0	(Hamscher, 2005)
Tetracycline	117.0	(Hamscher, 2005)
Tetracycline	105.0	(Hu, 2010)
Tetracycline	2.5	(Hu, 2010)
Tetracycline	198.7	(Blackwell, 2005)
Tetracycline	94.2	(Blackwell, 2005)
Tetracycline	105.0	(Watanabe, 2010)
Tetracycline	74.4	(Li, 2011)
Tetracycline	60.2	(Li, 2011)
Tetracycline	24.6	(Li, 2011)
Tetracycline	553.0	(Li, 2011)
Tetracycline	2.9	(Ok, 2011)

▷ Ecotoxicology and Environmental Risks

Ecotoxicological data for aquatic organisms were retrieved from Wikipharma (www.wikipharma.org) in Nov. 2012 and are visualised together with the monitoring data from

the aquatic environment in Figure 15[397]. The lower confidence limit of the 5% percentile of the resulting species-sensitivity distribution (SSD), based on NOECs is termed the HC5 ("hazardous concentration for 5% of the species), which is 3.3 nmol/L. The lower 95% confidence interval of the 5% percentile of the EC50 values is at 60 nmol/L, the factor of 20 being a quite typical average difference between median and low-level effects.



Source: Data were retrieved from Wikipharma (www.wikipharma.org, Nov. 2012).

Figure 15: Species-sensitivity distribution for tetracyclines in the aquatic environment

According to the REACH guidance document (ECHA, 2008), an assessment factor between 5 and 1 should be applied to this concentration in order to determine the final Predicted No Effect Concentration (PNEC), which would hence range between 3.3 nmol/L and 0.66 nmol/L for tetracyclines. It should be emphasised that for the HC5 calculation the ecotoxicological data for all the different tetracyclines were pooled, i.e. it was assumed that all members of the group have a similar ecotoxicological profile.

As can be seen from Figure 15, median concentrations in natural waters are generally a factor of roughly ten below the HC5 of 3.3 nmol/L, with the exception of Oxytetracline for which a median concentration of 3 nmol/L (1.34 µg/L) is detected in natural waters. However, concentrations in

397 Data were retrieved from Wikipharma (www.wikipharma.org, Nov. 2012). Data for all different tetracyclines were pooled together for the determination of the species sensitivity distribution, i.e. it was assumed that there are no fundamental differences in the ecotoxicological properties of the various tetracyclines. Solid squares indicate EC50 values, open circles indicate NOEC values. The HC5 of 0.0033 µmol/L is based on the lower 95% confidence interval of the lower 5% percentile, as derived from the log-linear fit to the distribution of NOEC-data. The lower 95% confidence interval of the 5% percentile of the EC50 values is at 0.06 µmol/L. Exposure data were retrieved from (Segurra,2009) and are listed separately in Table 27 of the present report. Red symbols indicate concentrations in natural waters (median to the left, maximum to the right), green symbols refer to concentrations in wastewaters (median to the left, maximum to the right). No exposure study on Minocycline occurrence in natural waters was identified by Segurra et al.(Segura, 2009)

natural waters often exceed 0.66 nmol/L, i.e. the PNEC when the larger assessment factor of 5 is applied. This is the case for Oxytetracycline, Chlortetracycline, Demeclocycline, and Tetracycline.

Taken together, these data clearly indicate that several members of the Tetracycline family are a potential risk to the aquatic environment at currently detected concentrations. In particular, Oxytetracycline seems to regularly exceed environmentally acceptable concentrations. On the other hand, Meclocycline and Doxycycline have not been found in environmentally hazardous concentrations. Concentrations in wastewater are regularly exceeding the PNEC, the actual environmental risk hence depends on the type of effluent analysed (influent, effluent), (bio)transformation and dilution in the recipient stream. It should also be pointed out that Segurra and colleagues did not describe any monitoring studies for Metacycline, Rolitetracycline, Tigecycline, and Penimepicycline. The amount of available monitoring data is also limited for Demeclocycline, Meclocycline and Minocycline (less than 10 published studies).

The broad range of detected concentrations, especially for Tetracycline, Oxytetracycline and Chlortetracycline, might indicate the necessity of scenario-specific investigation of the actual risk for the aquatic environment.

Ecotoxicological data for tetracyclines for terrestrial organisms, except soil bacteria, are comparatively scarce. Available data usually indicate EC50 values in the range of several tens to hundreds of mg/kg, i.e. in concentration far above the environmentally detected concentrations, see Figure 15. For example Baguer and colleagues (2000) provided EC50 and NOEC values exceeding 1 g Oxytetracycline /kg dry weight for chronic toxicity to *Folsomia fimetaria* (springtail), *Enchytraeus crypticus* (white pot-worm) and *Aporrectodea caliginosa* (earthworm). The genotoxicity of Tetracycline was investigated by Xie and coworkers (Xie, 2011) in a wheat bioassay, in which effects on the mitotic index were observed in concentrations between 50–300 mg/L. Boleas and coworkers (Boleas, 2005) did not find any mortality of *Eisenia foetida* (earthworms) in Oxytetracycline-spiked soil at concentrations of up to 100 mg/kg in the topsoil layer. However, bacterial activity was significantly but transiently influenced in the same study. A similar pattern, i.e. a comparatively high sensitivity of soil bacteria in comparison to higher organisms (plants) was also described by Liu et al (Liu, 2009). In this study Chlortetracycline and Tetracycline affected seedling height and root length of rice and cucumber significantly only at concentrations in excess of 300 mg/kg.

In summary, the available data on the toxicity of tetracyclines to higher soil organisms, animals as well as plants, do not indicate any substantial environmental risk, while environmentally realistic concentrations have a measurable impact on soil microbes and microbial enzymes. Whether this might lead to ecologically relevant, indirect, effects on soil functions and ecosystem services is currently unknown.

- **Human health aspects**

No studies on concentrations of tetracyclines in drinking water were found; however, tetracyclines in the environment, as all other antibiotics, might add to the risk of antibiotic resistance development (see discussion in section 6.2.1). No information is available that would indicate an additional risk for human health from direct or indirect environmental exposure (drinking water, food).

Procedural aspects, ERA and risk mitigation options

Tetracycline, Oxytetracycline and Chlortetracycline were the three most heavily used tetracyclines in the UK in 2000 (Sarmah, 2006). Even if Tetracycline and its derivatives are used in veterinary medicine in very large quantities (50% of the global veterinary antibiotics), the procedural information about the market authorisation of its numerous different products is extremely limited. Details on the status of each of the listed tetracyclines were compiled from the EMA website at:

www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp

The majority of products containing Tetracycline, Oxytetracycline or Chlortetracycline have reached the veterinary market through national procedures, without the obligation to perform an ERA. Very limited data are available, as even public report assessments (PAR) are unobtainable. Even products authorised through mutual recognition or decentralised procedures (not distinguishable based on the collected information) do not refer to the ERA they should have performed.

Tigecycline (market name Tygacil) is the only compound from ATC group J01A that was registered via the centralised authorisation procedure (Decision (2006)1759 of 24/04/2006, Marketing authorisation according to Article 13 of Regulation (EC) No 726/2004)[398]. Current market authorisation holder is Pfizer Limited (Community Register of medicinal products¸ accessed 17.11.2012). The only pharmaceutical form currently marketed is a powder for solution for infusion (i.e. intravenous use), EU number EU/1/06/336/001. The corresponding EPAR is available from the EMA website (EMA, 2013b), but does not contain any specific information related to ecotoxicology or chronic human exposure via the environment. EMA's documentation on the authorisation of Tigecycline simply contains the following summary assessment: "*The environmental risk assessment of tigecycline followed primarily the draft of guidelines related to this issue. From the results obtained, it is concluded that tigecycline for injection is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.*" No further details on environmental risks are available from EMA's website.

Some information on Tetracycline can be found through the procedural authorisation of Tetracycline intended for human use, for example the Lymecycline which was authorised on September 13th 2012 via a decentralised procedure (RMS was UK and CMS were Belgium, Denmark, Finland, France, Ireland, Italy, Norway, and Sweden). In the PAR, they indicated that "no new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Lymecycline 408mg Capsules outweigh the risks". Being a generic medicinal product of Tetralysal 300mg Capsules (which were initially granted in Denmark in May 1962), suitable justification has been provided for not submitting a risk management plan for this product and no new non-clinical studies were conducted.

398 Tigecycline authorisation details available at : www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000644/human_med_001118.jsp&mid=WC0b01ac0580 01d124,

Table 29 present other examples of medicinal products containing tetracyclines along with their corresponding procedures.

Table 29: Examples of medicinal products containing tetracyclines and corresponding procedures

Pulmodox 5% Premix Active substance : doxyxycline 50mg/g	Mutual recognition or decentralised (not clearly mentioned) RMS: France CMS: Austia, Denmark, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden	Date of outcome: 17/01/2006	No There is not any reference to an ERA	No	No PAR
CTC Spray 2.45 % w/w for cattle, sheep and pigs Active substance: Chlortetracycline 2.45% w/w (3.21 g)	Mutual recognition or decentralised (not clearly mentioned) RMS: The Netherlands CMS: Austria , Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Spain	Date of renewal of the authorisation: 20/03/2009	No There is not any reference to an ERA	No but The section on dosage will now include the following statement: "Note. Prior to the administration of Chlortetracycline, the sensitivity of the pathogen is to be established (antibiogram). This applies especially to suspected infections with Escherichia coli and Salmonella typhimurium where already very high rates of Tetracycline resistance have been observed."	No PAR

U-tab 2000 mg intrauterine tablet for cattle Active substance : doxyxycline hydrochloride 2000 mg	Mutual recognition or decentralised (not clearly mentioned) RMS : Germany CMS : Austria, Netherlands, Poland, UK	Date of outcome: 21/03/2011	No There is not any reference to an ERA	No	No PAR
OXYTETRACYCLINE 20% INOUKO injectable solution Active substance: Oxytetracycline 200mg	National procedure[399]	Date of authorisation: 04/12/1998	No There is not any reference to an ERA	No	No PAR
OXYTETRACYCLINE 10% VETOQUINOL injectable solution Active substance: Oxytetracycline dihydrate 100mg	National procedure	Date of authorisation: 07/03/1984	No There is not any reference to an ERA	No	No PAR

[399] www.docstoc.com/docs/35314370/Sheet1---wwwmoagovcy

Alamycin LA injectable 100mL Active substance: Oxytetracycline dihydrate 100mg	National procedure (Ireland)	Date of authorisation: 20/10/1993 Date of renewal: 30/09/2008	No There is not any reference to an ERA	No	No PAR
Doxycycline 50% WSP and associated names (doxycycline hyclate 500mg/g)	National procedure[400] (Belgium, Bulgaria, Denmark, Greece, Hungary, Lithuania, The Netherlands, Poland, Portugal, Romania, Finland, France, Germany, Italy, Latvia, Slovakia, UK)	Date of authorisation: 13/07/2011	No There is not any reference to an ERA	No	No PAR
DOXI-10 S.P. PREMIX Active substance: doxycycline hyclate 10 %	Mutual recognition or decentralised (not clearly mentioned) RMS : Spain CMS : Bulgaria, Poland,	Date of authorisation: 23/09/2011	No There isn't any reference to an ERA	No	No PAR

[400] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:316:0018:0193:EN:PDF

Romania

Tylosin

Active substance/product information

Tylosin is a macrolide antibiotic that is active against a number of Gram-positive and Gram-negative bacteria. It is a mixture of four macrolide antibiotics produced by a strain of *Streptomyces fradiae*, with the main (and the most active) component of the mixture being Tylosin A (Lewicki, 2006).

This case study focuses on the pharmaceutical product Pharmasin 100% W/W Water Soluble Granules® (generic of the reference product Tylan W.O®). This veterinary product was delivered via prescriptions to treat intestinal and respiratory diseases in calves, pigs, chickens and turkeys. It was administered orally in the form of granules dissolved in drinking water[401].

Scientific information

▶ Environmental aspects

▷ Contamination pathway and behaviour in environment

Tylosin can be released into the environment through various waste streams, from its manufacture to disposal. Main contamination pathway, however, could be animal excretions and the use of manure in farming (Boxall, 2003)[402], even though it is said to be extensively metabolised at these points. Most of the residues are excreted in faeces predominantly consisting of Tylosin (factor A), relomycin (factor D) and dihydrodesmycosin[403].

In the soils, Tylosin biodegrades rapidly (Hu, 2007) (De Liguoro, 2003) (half-life of about 2 days in soil) and has low to no mobility (high Koc) (Rabølle, 2000). If released into water, Tylosin is expected to be adsorbed in suspended solids and sediments.

▷ Exposure

Terrestrial and aquatic organisms may be exposed to Tylosin through the contamination of their respective environmental compartments. This compound namely has been reported in drinking water (Watanabe, 2010) and groundwater (Hughes, 2013). Hughes et al. (2013) reported median concentrations in freshwater ecosystems of 12.5 ng/L and max concentrations of 280 ng/L. They highlight a detection frequency of Tylosin of about 35.4% (no. positive detections/no. samples analysed) (Baguer, 2000).

401 Summary of product characteristics (MRI) http://mri.medagencies.org/download/NL_V_0159_001_FinalSPC.pdf
402 Tylosin, The Toxicology Data Network of the US National Library of Medicine Available at : http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7022
403 www.imb.ie/images/uploaded/swedocuments/LicenseSPC_10782-012-001_08042011140648.pdf

▷ Impacts

Acute toxicity has been observed on algae and risks may exist for cyanobacteria and some plant species (radish and zucchinis). It is reported in the Annexes to the opinion of EMA following the referral for Pharmasin[404] as well as in the scientific literature.

In **soil fauna**, no toxicity was observed, based on:

- tests on 3 species (Baguer, 2000) giving:
  - NOECs ≈ 4000 mg/kg soil;
  - EC_{50} ≈ 5000 mg/kg soil;
  - PEC ≈ 5 mg/kg soil;
- ERA tests giving PEC/PNEC< 1 for all four target animal species[404].

In algae, no toxicity was observed in *Daphnia Magna:*

- LOEC ≈ 700 mg/L (Wollenberger, 2000)
- $EC_{50, 48h}$ ≈ 700 mg/L (Wollenberger, 2000) (so PNEC ≈ 700 µg/L)
- PEC ≈ 0.001 µg/L (Wollenberger, 2000)

However, acute toxicity was observed on two other species, with EC_{50}s of 0.03 mg/L and 1.4 mg/L (Halling-Sørensen, 2000).

In bacteria, EMA could not exclude a risk for cyanobacteria based on ERA.

In terrestrial plants, there is no or low absorption of Tylosin:

- tests on carrots and lettuce giving DT_{50}s < 0.5 µg/kg while PEC soil ≈ 1.5 µg/kg (Boxall, 2006)
- tests on green onion and corn show no absorption (Kumar, 2005).

Low toxicity is observed on plant growth with tests on rice and cucumber: EC_{50} ≈ 500 mg/kg soil and LOEC ≈ 300 mg/kg soil (Liu, 2009). However, a potential risk was estimated for radish (EC50 ≈ 150 mg/kg) and zucchinis (lowest NOEC ≈ 45 mg/kg and LOEC ≈ 91 mg/kg) , with PEC/PNEC > 1[404].

▶ Human health: exposure and impacts

▷ Exposure

Humans may be exposed to Tylosin through the ingestion of contaminated food and drinking water, although limited information exists. Tylosin was measured in finished drinking water of two Italian cities at 0.6 and 1.7 ng/L) (Zuccato, 2000).

▷ Impacts

Severe toxicity on human heath has not been reported. However, chronic exposure to low dose of Tylosin is likely to be involved in the emergence of *Erythromycin-Resistant Campylobacter*,

404 Annexes to the opinion of the EMA following the referral for Pharmasin (EMA, 2010b) www.emea.europa.eu/docs/en_GB/document_library/Referrals_document/Pharmasin_33/WC500090085.pdf

which constitutes a possible hazard to human health (Lin, 2007) (Barton, 2000). Since the ban of Tylosin as a growth promoter in food animals, marked effect was observed on resistance rates in enterococci in the faecal flora of man and animals (Phillips, 2004).

Procedural aspects, ERA and risk mitigation options

A marketing authorisation dossier for Pharmasin® 100% W/W Water Soluble Granules was submitted in 2007 following a decentralised procedure, in the framework of Article 32 of Directive 2001/82/EC, as amended. The RMS was The Netherlands. CMS consisted of Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Spain, Hungary, Ireland, Italy, Poland, Portugal, Romania and United Kingdom.

An ERA was elaborated as a part of the application of the Marketing authorisation. ERA is not available on the EMA website, but primary results are included in Annex II to the EPAR in the scientific conclusions (EMA, 2010b)[405]. The Phase I environmental risk assessment following the VICH (Veterinary International Co-operation on Harmonisation) guideline (EMA, 2000) results in PEC in soil for Pharmasin 100% W/W Water Soluble Granules for all target species above 100µg/kg which is the threshold above which pharmaceutical products must undergo a Phase II assessment.

Species	PECs soil
calves	3199 µg/kg
pigs	1738µg/kg
broilers	4435µg/kg
turkeys	2210µg/kg

A Phase II assessment was therefore required.

Concentrations of Tylosin in surface water and groundwater were estimated by the applicant using methods, described in the CVMP Revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products (EMA, 2007). PEC groundwater values for pigs, broilers, turkey and calves were calculated respectively as 6.43, 16.4, 8.17 and 11.8 µg/L. PEC surface water values for the same species were calculated as 2.14, 5.47, 2.72 and 3.93 µg/L respectively. Yet, on 29 April 2008 the Netherlands referred the matter to EMA due to concerns raised by Germany that Tylosin may present a potential serious risk to the environment, particularly to algae and terrestrial plants, based on available data from former applications. The referral procedure started on 14 May 2008 and on 16 September 2008, the CVMP agreed on a list of outstanding issues to be clarified by the applicant.

The referral concerned the effects on the terrestrial compartment and the effects on the aquatic compartment, particularly the controversial adequacy of the data provided. Although the applicant generally followed VICH guidelines, the CVMP considered in its 10 December 2008 opinion that the nitrogen transformation study and the study with terrestrial plants were inadequate to waive potential risks for soil microorganisms and plants. In the aquatic environment, based on the information provided, a risk for cyanobacteria cannot be ruled out.

405 ANNEX II - Scientific conclusions and grounds for the refusal to grant new marketing authorisations and for the revocation of existing marketing authorisations for Pharmasin® 100% W/W Water Soluble Granules. Available at : www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pharmasin_33/WC500090085.pdf

Without a tier II-B assessment, no further conclusions concerning the risk for cyanobacteria could be drawn.

Extensive information about scientific conclusions and grounds for the refusal to grant new marketing authorisations and for the revocation of existing marketing authorisations is presented in Annex II to EMA Opinion following an Article 33(4)1 referral for Pharmasin (EMA, 2010b)[405]. In particular, this annex specifies and discusses methodologies used, compliance with ERA guidelines and standardised methods, and key results and shortcomings of the ERA proposed by the applicant.

During its 9-11 December 2008 meeting, the CVMP, in light of the overall data submitted and the scientific discussion within the Committee, unanimously concluded that the application did not satisfy the criteria for authorisation in respect of environmental risk, based on incompleteness of the dossier. The CVMP considered that data was missing and results of studies carried out were unreliable; a conclusive assessment of the risk to the terrestrial and aquatic compartments therefore could not be carried out. The CVMP thus considered that restricting the SPC by removing indications and/or target species was not sufficient because of the inappropriate nature of the current indications, in particular due to the absence of reliable effects data for plants and microorganisms means. Despite a critical re-examination requested by the applicant, the CVMP opinion on the invalidity of the data provided was not revised. The CVMP recommended the refusal of the granting of the marketing authorisations for Pharmasin® 100% W/W Water Soluble Granules and associated names. Application was refused on 8 January 2010. The CVMP also recommended the revocation of the marketing authorisations for the above-mentioned products that already were granted through national procedures in Austria, Ireland, the Netherlands and the United Kingdom.

However, as the refusal was based on dossier incompleteness, a new MA application was later introduced (with the Netherlands as RMS) and the MA for Pharmasin® 100% W/W Water Soluble Granules was ultimately granted[406].

406 See http://mri.medagencies.org/Veterinary/Product/Details/234; the SPC is available at http://mri.medagencies.org/download/NL_V_0159_001_FinalSPC.pdf

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