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*“State-of-art review of policy instruments  
to limit the discharge of pharmaceutical products  
into European waters”*

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## Abbreviations

APIs	Active Pharmaceutical Ingredients
BAT	Best Available Technique
BLAC	German Federal and States' Committee for the Safety of Chemicals ( <i>Bund/Länderausschuss für Chemikaliensicherheit</i> )
BREFs	BAT Reference Documents
DWD	Drinking Water Directive
EA	Environmental Agency (UK)
EIA	Environmental Impact Assessment
EIC	Environmental Introduction Concentration
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
Euratom	European Atomic Energy Community
IPPC	Integrated Pollution Prevention and Control
KNAPPE	EU Project "Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters" PEC Predicted Environmental Concentration
LIF	Swedish Association of the Pharmaceutical Industry
MHRA	Medicines and Healthcare Products Regulatory Agency
MPA	Swedish Medical Products Agency
MS	Member State
NOEC	No Observed Effect Concentration
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effects Concentration
PPs	Pharmaceutical products
RBMP	River Basin Management Plan
REACH	Regulation on the Registration, Evaluation, Authorization and Restriction of Chemicals ((EC) No. 1907/2006)
SRU	German Council of Environmental Advisors ( <i>Sachverständigenrat für Umweltfragen</i> )
STP	Sewage Treatment Plants
UWWTD	Urban Wastewater Treatment Directive
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products
VMD	Veterinary Medicines Directorate
VMPs	Veterinary Medicinal Products
WFD	Water Framework Directive



# 1 Introduction

## 1.1 Rationale

Scientists agree that nowadays there is an increased presence of pharmaceutical products (PPs) in the environment, including the aquatic one. However, knowledge on the nature and extent of the environmental impact of PPs is still limited. Few cases of significant environmental impact of PPs have been confirmed so far. Especially some classes of PPs can act as endocrine disruptors, which have been linked to abnormalities and impaired reproductive performance in some species, mainly fish.

Despite our limited current understanding of this emerging environmental issue, the scientific community tends to agree that we should already explore ways of limiting the input of PPs into the environment, anticipating thus action needed in the near future.

Moreover, although the environmental concentration of PPs is considered to be too low to have an effect on human health, public demand for drinking water of good quality - free of chemical substances - cannot be overlooked by water managers. The presence of PPs in water also remains for some an issue of concern with respect to human health, especially when bearing in mind the following: the availability of occurrence data for PPs in drinking water has been very limited so far; food grown on sewage- or manure-amended soil may contain substantially higher concentrations than those in drinking water; the increasing spread of antibiotic-resistant bacteria can pose a health risk for humans; the lack of knowledge on risk to human health from chronic exposure to PPs designed for short-term use; the lack of knowledge on risk to human health from exposure routes differing from the intended clinical routes (e.g. ingestion of PPs intended for dermal use only); the lack of knowledge on risk from unintended, unexpected exposure of certain human sub-populations to PPs that they should actively avoid (e.g. drugs contra-indicated during pregnancy) (Daughton & Ruhoy, 2007; SRU, 2007).

In this context, one of the main aims of the EU KNAPPE project is to bundle and extend the research on the occurrence of PPs in the aquatic environment as well as on the environmental and health impacts related to PPs.

The present report is part of WP3 of KNAPPE which deals with policy instruments and ultimately with the development of cornerstones of a possible EU prevention action to limit PP discharge into water. The work of WP3 will be combined with relevant conclusions and recommendations of the technical workpackages of the project, especially those dealing with PP occurrence in the environment, limits of current wastewater treatment, and health and environmental impacts of PPs. New technical and scientific knowledge is crucial for making any proposals on the regulatory and policy framework. Policy proposals through the KNAPPE project will not only be limited to regulatory action, but will also point to other forms of instruments (e.g. economic instruments and voluntary approaches) which can contribute to limiting PP discharge without increasing the regulatory burden.

## 1.2 Objectives and scope

The present study aims at reviewing key existing policy instruments and approaches at EU level and in selected Member States, which are relevant to limiting the discharge of pharmaceutical products (PPs) into the water environment. Policies treated in this state-of-the-art review address issues of authorisation of PPs, pollution prevention, wastewater treatment as well as monitoring of environmental quality.

The review pays attention to regulations directly relevant to medicinal products but also to broader environmental protection policy. In this context, it seeks to establish links to important water and other natural resource protection policies, such as the EU Water Framework Directive, the Groundwater Directive, the European Soil Strategy and others.

The analysis should serve as a basis for the identification of possible gaps in current approaches. Ultimately, it will contribute to the formulation of recommendations for a future instrument mix at EU level (of regulatory and non-regulatory approaches) to deal with the issue of PPs in the water environment.

Given that the focus of other work-packages in the KNAPPE project is on human PPs, this state-of-art review mainly concentrates on instruments related to human medicine. Policies on animal medicine are treated less extensively and only in so far as they are relevant to the water environment.

The issue of metabolites is not addressed, as this issue is too complex to be addressed from a policy perspective with the resources provided in this project.

To a large extent, the analyses of EU medicinal regulations carried out in previous EU-funded projects (e.g. Poseidon, ERApharm) have been used as a starting point for parts of this review. Thus, the sections on EU medicinal regulations, including environmental risk assessment requirements for PPs, frequently refer to previous EU-funded publications for more details.

New aspects put forward relate to the recently released new EU guidelines on environmental risk assessment, to the links provided between PPs and EU environmental protection policies, and to the review of the state-of-play in selected Member States. The paper also reviews and summarises ongoing discussions and expert commentaries on the current EU policy framework for limiting the discharge of PPs into water.

### **1.3 Structure of this paper**

The following Chapter 2 refers to the EU policy framework relevant to the presence of pharmaceutical products (PPs) in the environment. Section 2.1 deals with EU regulations for the authorisation of medicinal products, while Section 2.2 explores links between the issue of pharmaceutical products in the environment and EU environmental and water protection policies.

Chapter 3 presents the state-of-play in three European countries (UK, Germany and Sweden) concerning their policy approaches and supportive activities on the issue of pharmaceutical products in the environment (especially water).

Chapter 4 is an integrated discussion of the current policy framework, based on the findings of the present review as well as existing expert literature and discussion papers.

## 2 Policy framework at EU level

This chapter describes the EU policy framework relevant to the presence of pharmaceutical products (PPs) in the environment. Firstly, the chapter describes the development of regulations for the authorisation of medicinal products; progressively these regulations have given more emphasis to the environmental risk assessment of PPs. Secondly, the chapter explores existing and potential links of pharmaceutical products and current EU policies on environmental and water protection.

### 2.1 Medicinal regulations & policies

#### 2.1.1 Product authorisation and environment risk assessment

##### Development of regulations

Directive 65/65/EEC on human medicine first set the legal requirements for the European authorisation process of pharmaceutical products (PPs). In order to obtain a marketing authorisation for a new product, its quality, safety and efficacy must be demonstrated by the pharmaceutical company. Although the Directive 65/65/EEC already recognised that an application for marketing authorisation of a medicinal product for human use should be accompanied, if applicable, by an indication of any potential risks for the environment (Montforts & de Knecht, 2002), focus of attention in this early regulatory phase was on the safety of patients, not on the environment. Environmental concerns in the authorisation process were only considered with more intensity much later.

The environmental risk assessment of animal and human pharmaceuticals was established with the EC Directives 90/676/EEC and 93/39/EEC respectively. The environmental risk assessment (ERA) introduced is relevant to the consumption phase of PPs. The assessment of environmental risks arising from the synthesis and manufacture of medicinal products is governed by the chemical legislation.

Later on, the 1990 and 1993 pharmaceutical directives were replaced by new codified Directives in 2001<sup>1</sup> and most recently by new amending directives in 2004 (Directive 2004/27/EC on human medicine, 2004/28/EC on veterinary medicine, and the new regulation EC/726/2004 establishing environmental risk assessment for medicine containing or consisting of genetically modified organisms<sup>2</sup>). These new regulations came into force in the end of 2005 (Koschorreck & Apel, 2006; Knacker et al., 2006). Therefore, current EU regulations on pharmaceutical products and on the environmental risk assessment in their authorisation process are quite recent. Although separate regulations exist for “human medicinal products” and “veterinary medicinal products”, these two categories of PPs are addressed in consecutive regulations which are based on the same principles and are highly similar in content.

According to Directive 2004/27/EC on human PPs, for all new authorisations of PPs, the environmental effects must be examined and this assessment must accompany the authorisation application. The environmental risk assessment typically involves the generation of data on the environmental exposure and ecotoxicity of PPs. Prior to 2004, detailed environmental risk assessment was only carried out in exceptional cases for human medicine

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<sup>1</sup> Directive 2001/82/EC for veterinary medicine and Directive 2001/83/EC for human medicine.

<sup>2</sup> These medicinal products would not undergo the environmental risk assessment of normal medicinal products, but rather follow a “procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms”.

(Holzmann, 2005). However, the granting of a marketing authorisation of human medicine cannot be refused using the environmental impact as criterion.

For veterinary PPs, the situation is different. Contrary to human PPs, the granting of a marketing authorisation of a veterinary medicine can be denied due to an unacceptable risk for the environment (Koschorrek & Apel, 2006). The 2004 EU regulatory amendments indeed introduced certain key changes in the authorisation of veterinary medicines. The criterion of environmental safety has been given the same weight as consumer safety in the concluding risk-benefit assessment and, therefore, can decide about the authorisation or non-authorisation of a new veterinary PP (Holzmann, 2005).

### **Guidelines for environmental assessment of PPs**

In the EU, specific guidelines recommend the scope and the actual procedure for the environmental assessment of medicinal products, before these are evaluated for marketing approval. Currently, the environmental risk assessment (ERA) of human pharmaceuticals is based on the Guidelines of the European Agency for the Evaluation of Medicinal Products (EMA)<sup>3</sup> and the environmental impact assessment (EIA) of veterinary pharmaceuticals is based on the VICH guidance (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products).<sup>4</sup>

For **human medicinal products**, the current guidance document, adopted by the EMA Committee for Human Medicinal Products, came into effect in the end of 2006 (discussions relating to this guidance started in the late 1990s). According to this document, an ERA is required for all new marketing authorisation applications for medicinal products, for type II variations (major changes to the marketing authorisation) and for extension applications if there is an increase in environmental exposure. An ERA is not required for renewals or type IA/IB variations (minor changes to the marketing authorisation).<sup>5</sup> There may also be cases in which the absence of an ERA could be justified, e.g. marketing authorisation applications for generic medicinal products or type II variations. Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents. For marketing authorisation applications for radio-pharmaceutical precursors for radio-labelling and radio-pharmaceuticals, additional requirements on emission standards for radiation set by Council Directives 96/29/Euratom and 97/43/Euratom should be taken into account (CHMP, 2006).

The guidance document follows a 2-phased structure of assessment (see Figure 1):

- In Phase I, the drug concentration expected to occur in the aquatic environment is calculated (predicted environmental concentration (PEC<sub>surfacewater</sub>)). If the PEC is below a

<sup>3</sup> Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency. London, 01 June 2006. Doc. Ref. EMA/CHMP/SWP/4447/00.

<sup>4</sup> Guidance for industry: Environmental Impact Assessment (EIAs) for veterinary medicinal products (VMPs). VICH International Cooperation for on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. Phase I (VICH GL6) and Phase II (VICH GL38).

<sup>5</sup> Variations are divided into three types. Type IA and IB variations are minor changes and type II variations are major changes to the marketing authorisation.

Type IA/IB variations are in fact notifications, i.e. applicants just inform regulatory authorities and implement the changes without delay or approval. Examples are change in the name or address of the marketing authorisation holder or the manufacturer, change in the name of the medicinal product, change in the name of the active substance, minor change in the manufacturing process of the active substance, etc.

Type II variations are defined as changes that are neither type IA, type IB nor new applications. Examples include change in the manufacturing process of the active substance that could affect efficacy, deletions in security information, deletions of contraindications, changes in adverse reactions, etc.



defined action limit of  $0.01 \mu\text{g l}^{-1}$ , it is assumed that this specific medicinal product is unlikely to represent a risk for the environment. Thus, the assessment procedure does not continue. If the calculated PEC is equal or above this action limit, a Phase II environmental fate and effects analysis is required. In some cases, the action limit may not be applicable. Some drug substances may affect the reproduction of vertebrate or lower animals at concentrations lower than  $0.01 \mu\text{g l}^{-1}$ . These substances should enter Phase II and a tailored risk assessment strategy should be followed that addresses its specific mechanism of action.

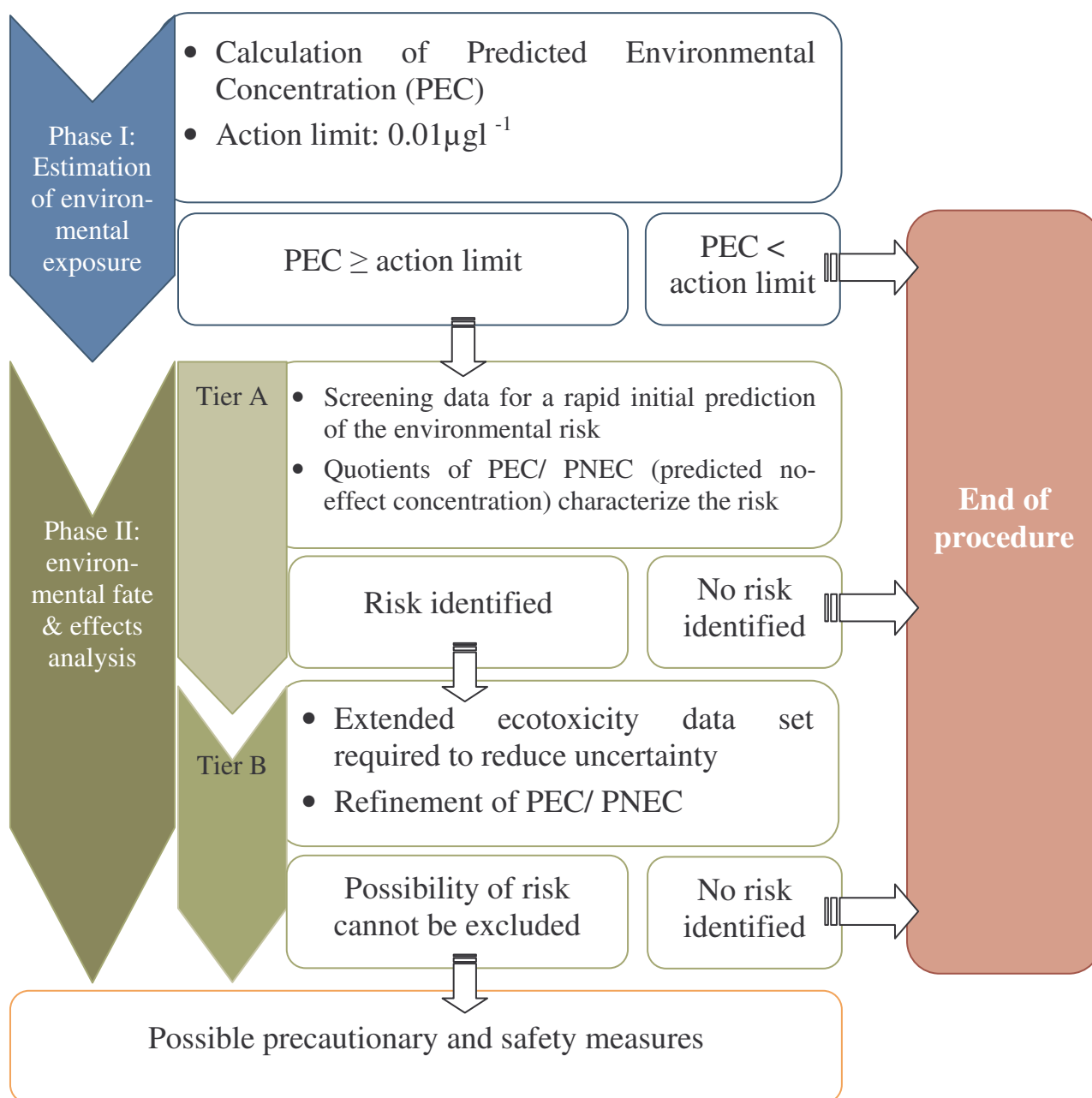
- In Phase II, information on the physical, chemical and toxicological properties are obtained and assessed in relation to the extent of the environmental exposure. Phase II is split into Tier A and Tier B. A screening information base set of data in Tier A allows for a rapid prediction of the environmental risk linked to the use of the product. Quotients of PEC/PNEC characterise the risk for the aquatic compartment and for microorganisms. PNEC is the predicted no-effect concentration, which is derived from the lowest no observed effect concentration (NOEC) or dose-response result of a set of laboratory ecotoxicity studies representing the aquatic or terrestrial compartment. Certain additional assessment criteria, such as half-life biodegradation, are given with fate data. If at Tier A no risk is identified, the assessment is complete. If at Tier A risk is identified, the subsequent Tier B level requires an extended ecotoxicity data set, which should allow for a reduction of uncertainty and addressing data gaps. Tier B is the ultimate step in the risk assessment and resembles an iterative process of PEC and PNEC refinement.

As concerns the specific environmental compartments targeted by the ERA for human medicine, it should be noted that in Phase I, the PEC calculation is restricted to the aquatic compartment. In Phase II (Tier A), standard long-term toxicity tests on fish, daphnia and algae are proposed to determine the  $\text{PNEC}_{\text{water}}$ . An exposure assessment for groundwater is also required, since entry into the groundwater via bank filtration is considered. Furthermore, the fate of the substance in the sewage treatment plant (STP) is investigated via a biodegradability test. The fate of substances which are not readily biodegradable should be investigated in a water-sediment study. It is assumed that a substance with high adsorption coefficient is retained in the STP and may reach the terrestrial compartment with land spreading of sewage sludge. In this case, an environmental assessment of the drug substance in the terrestrial compartment should be conducted, unless the substance is readily biodegradable. The terrestrial risk assessment complements the aquatic risk assessment and does not replace it (CHMP, 2006).

In general, in Tier B of Phase II, a base set of tests investigating biodegradation in soil, toxicity to soil invertebrates and acute effects on terrestrial plants and microorganisms should be conducted. If a substance is not readily biodegradable and if the results from the water-sediment study demonstrate significant shifting of the drug substance to the sediment, effects on sediment organisms should be investigated (CHMP, 2006).

In the end of the ERA procedure, if the possibility of environmental risk cannot be excluded, specific arrangements to limit risk should be envisaged on a case-by-case basis (possible precautionary and safety measures). In any event, in the case of human medicine, environmental impacts can not constitute a criterion for refusal of a marketing authorisation according to Directive 2004/27/EC.

More details on the ERA process of human medicine can be found in the EMEA 2006 guideline (CHMP, 2006) as well as in the literature (Kümmerer (Ed.), 2004; Koschorreck & Apel, 2006; Umweltbundesamt (Ed.), 2005).

**Figure 1 Environmental risk assessment for human pharmaceutical products**

For **veterinary medicinal products**, first draft EU guidelines on their EIA existed already in the early 1990s. The VICH guideline on Phase I assessment currently in force dates back to 2001. In 2005, the VICH Phase II guidelines also came into force in the EU. In 2006, an additional supporting guideline was published by the EMEA, to provide additional, more specific technical guidance on the environmental impact assessment of veterinary medicine. This guideline is also intended to harmonise the interpretation of the VICH guidelines by EU Member States, thus strengthening predictability and transparency of the outcome of an environmental impact assessment.

According to the present guidelines for veterinary medicine, an EIA is mandatory for all new applications, independent of the application procedure (central or national marketing authorisation) and type (“full”, “generic” etc.), and is therefore required for all marketing authorisations submitted in the EU irrespective of the underlying legal basis. In respect to renewals, the legal provisions require “a re-evaluation of the risk-benefit balance”. Further

guidance on the interpretation of the data requirements, in particular in respect to marketing authorisation applications for generics, extensions and variations, as well as for renewals, is under development (CVMP, 2007).

The EIA for veterinary medicine follows the same 2-phased structure (Phase I and Phase II with Tiers A and B) as the ERA for human medicine (see Figure 1). However, some key differences do exist due to the different nature and areas of application of human and veterinary medicine.

For instance, in its Phase I the EIA for veterinary medicine is distinguished into an aquatic and a terrestrial branch, depending on whether the medicine is used to treat aquatic or terrestrial species. Distinct PECs are thus calculated for soil and water, while ecotoxicity studies are related respectively to aquatic species and terrestrial species (earthworms, microbes and plants). In the aquatic branch, the EIA continues beyond Phase I only if the environmental introduction concentration of the medicine ( $EIC_{\text{aquatic}}$ ) is calculated to be more than  $1 \mu\text{g/L}$ . In the terrestrial branch, the EIA continues beyond Phase I only if the predicted environmental concentration of the medicine in the soil ( $PEC_{\text{soil}}$ ) is calculated to be more than  $100 \mu\text{g/Kg}$ .

The Phase II guidance for veterinary medicine contains different sections for each of the following major branches: aquaculture, intensively reared terrestrial animals, and pasture animals. Exposure to both the terrestrial and aquatic compartment may be applicable to a particular medicine, depending on its route of environmental introduction. For instance, veterinary medicine administered to intensively reared animals has the potential to impact terrestrial non-target species directly, and non-target species in surface waters indirectly due to transport via water, including when adsorbed to soil particles and organic matter. In this case, due to possible leaching of active ingredients also into groundwater, it is necessary to calculate PECs both for surface and groundwater. Veterinary medicine used to treat pasture animals may also impact terrestrial non-target species, as well as non-target species in surface waters indirectly due to transport in water, including when adsorbed to soils. Therefore, also in the case of medicine for pasture animals, it is necessary to calculate PECs for both surface and groundwater.

In general, if there is evidence that there will be no exposure to a particular compartment (i.e. water, soil/sediment and dung), then it may be possible to waive studies for that compartment. However, sound scientific evidence should be presented in the marketing application dossier supporting the omission of these studies.

In the end of the EIA procedure for veterinary medicine, doubts about the acceptability of environmental risk can lead to changes of the characteristics of the product or of the area of application of the product, or even the refusal of marketing authorisation by the authorities.

### 2.1.2 Requirements for drug take-back schemes

In EU medicinal legislation, there are provisions to set up take-back schemes for unused and expired medicine in all Member States. Such take-back schemes are required by EU legislation since 2004.

Directive 2004/27/EC requires Member States to “ensure that appropriate collection systems are in place for human medicinal products that are unused or have expired” (Article 127b).<sup>6</sup> Reference to these collection systems is to be made on the labelling or package leaflet. These

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<sup>6</sup> European Parliament and the Council, Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. OJ L 136, 30.4.2004, p. 34.

systems had to be set up by the end of October 2005. As concerns veterinary products, the requirement to have appropriate collection systems dates from 2001 and was set out by Directive 2001/182/EC.<sup>7</sup>

Take-back schemes are, on the one hand, a means to reduce the increased presence of pharmaceuticals in the environment. If not disposed of in a sound way, unused and expired medicine can enter the water environment either directly when flushed down the toilet or indirectly via landfill leachate when disposed of in domestic solid waste (landfill leachate may contaminate groundwater if the landfill is not properly sealed, e.g. see relevant PP concentrations measured in groundwater in BLAC (2003)). On the other hand, take-back schemes also target the problem of unsafe pharmaceutical storage practices that can result in accidental poisonings and drug abuse. A brief review of drug take-back schemes in selected European countries (Sweden, France, UK, Germany) was made in Deliverable D5.1 of the KNAPPE project (Clark et al., 2007). All in all, the extent of the establishment and the degree of effectiveness of take-back schemes for human drugs is quite different among European countries. In-depth assessments of scheme effectiveness (estimated recovery rate of unused/expired drugs) are to a great extent missing. Individual available assessments often provide different and contradictory figures, pointing to the need for a more consistent approach that should be used in such evaluations. High levels of public awareness and education on the environmental consequences of the disposal of unused/expired drugs seem to be key for the success of such schemes. In Chapter 3 of the present report, we take a closer look at the drug take-back schemes of Germany, UK and Sweden.

## 2.2 Environmental protection regulations & policies

The following introduces key EU water policies, but also other environmental policies and initiatives which are related or could become related to the issue of PPs in the (aquatic) environment of Europe.

### 2.2.1 Water policies

#### *Water Framework Directive (WFD)*

The WFD 2000/60/EC requires reaching good status in all EU waters by 2015. For surface water, “good status” is defined as “the status achieved by a surface water body when both its ecological status and its chemical status are at least good“. In general, “good status” is defined as “slight changes in the values of the relevant quality elements as compared to the values found at closely undisturbed conditions”. The requirement of the WFD for good chemical status of water refers to the concentration of substances that are harmful to the ecosystem.

More than 100,000 different chemical substances are on the European market, 30.000 of which are produced in quantities over 1,000 kg per year (Schwarzenbach et al., 2006). During production, distribution, use, and through undeliberate loss many chemical substances enter the aquatic environment. Depending on their physico-chemical properties they can impair the ecosystem and pose a risk to human health. The WFD established two paths to minimize negative impacts of chemical substances on water bodies:

- 1) The WFD defined a list of priority substances that were considered to be particularly harmful to the aquatic environment on a European scale due to their toxicity, persistence, and bioaccumulation potential. Candidate substances for the list were selected on a "list-

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<sup>7</sup> European Parliament and the Council, 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. OJ L 311, 28.11.2001, p. 1.

based" approach, according to which the candidates were selected from official lists and monitoring programmes.<sup>8</sup> In summary, 658 substances were thus compiled (Klein et al., 1999). More than 300 of them were subject to risk assessment and extensive consultations before a final list of priority substances was published as Decision 2455/2001/EC; which then became Annex X of the Directive. It lists 33 priority substances (mostly organic pollutants (e.g. pesticides), but also some heavy metals and others), for which the Commission had to define environmental quality standards according to Article 16(7). The proposed Directive on environmental quality standards in the field of water policy is currently being negotiated; it is expected to be passed soon.

Member States must apply measures to progressively reduce the concentration of priority substances below the defined quality standards. In case of priority hazardous substances, measures have to aim at cessation or phasing-out of discharges.

At present, no pharmaceutical products are on the list of priority substances, with the exception of a few substances that have a broad spectrum of application and are also being used in the research and/or manufacturing of PPs.<sup>9</sup> The main reason for this can be seen in the selection process for the first list of priority substances, which dates back almost 10 years and was based on already existing official lists of pollutants. PPs, however, are often referred to as emerging pollutants, which means that their presence in and impact on the aquatic environment is just being discovered and researched. According to WFD Article 16(4), the European Commission is asked to review the list of priority substances every four years. In this process, it is expected to take account of all relevant information including recommendations from the European Scientific Committee on Toxicity, Ecotoxicity and the Environment, Member States, the European Parliament, the European Environment Agency, Community research programmes, and others. At the moment, the debate is ongoing on how exactly substances will be selected and assessed for the future update of the list of priority substances. It is clear, however, that by definition only PPs could be nominated for the list that exhibit toxic, persistent, and eventually bio-accumulative characteristics, and therefore have relevance on a supra-national scale. In fact, in current discussions on the proposed Directive on environmental quality standards amending the WFD, three pharmaceutical substances (carbamazepine, diclofenac and iopamidol) have been proposed as „subject to identification as possible priority substance”.<sup>10</sup>

Moreover, there is still considerable uncertainty regarding the risk of long-term uptake of presumably not harmful substance traces. In this context, the WFD puts emphasis on the precautionary principle, stating that especially in identifying priority hazardous substances, any potential adverse effects of the product should be taken into account and should lead to a scientific assessment of the risk (recital 11 and 44, WFD).

- 2) Member States are furthermore required to identify all other pollutants that are discharged in significant quantities in the river basin or sub-basin. They have to set quality standards

<sup>8</sup> List I and II of Council Directive 76/464/EEC, Annex 1A and 1D of the Third North Sea Conference (3. NSC), Priority lists 1-3 identified under Council Regulation No 793/93, OSPAR list of individual candidate substances, HELCOM lists of priority substances, Pesticides prioritised under Council Directive 91/414/EEC, Monitored substances not mentioned on any of the lists above (based on the monitoring data obtained from Member States) (Kleine et al. 1999, p. 7)

<sup>9</sup> E.g. trichloromethane (chloroform), trichloroethylene, tetrachloromethane, nonylphenol, naphthalene, mercury, dichloromethane, cadmium, chlorobenzene, anthracene, dichloroethane.

<sup>10</sup> European Parliament, Committee on the Environment, Public Health and Food Safety 2007: Compromise Amendments 1-3. Proposal for a Directive of the European Parliament and of the Council on environmental quality standards in the field of water policy and amending Directive 2000/60/EC. Draft report (PE 378.719v01-00), Anne Laperrouze. PE 386.558v01-00. 26.3.2007. [http://www.europarl.europa.eu/meetdocs/2004\\_2009/documents/dv/659/659305/659305en.pdf](http://www.europarl.europa.eu/meetdocs/2004_2009/documents/dv/659/659305/659305en.pdf).



for such river basin-specific pollutants, and take action to meet those quality standards by 2015 as part of good ecological status (Article 4, 11 and Annex V, WFD). This refers predominantly to substances listed in Annex VIII of the WFD which provides an indicative list of the main pollutants and inter alia covers “*substances and preparations, or the breakdown products of such, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect steroidogenic, thyroid, reproduction or other endocrine-related functions in or via the aquatic environment.*” (Annex VIII, No.4, WFD).

If PPs that enter the aquatic environment in significant quantities pose a risk to a water body due to their physico-chemical properties, they have to be covered by this requirement. However, as Member States (MS) are currently still in the drafting progress of the River Basin Management Plans (RBMPs), no such approach has been applied so far.

Consistently implemented, the two above-mentioned paths of the WFD provide the means to track down and minimise the effects of harmful chemical substances discharged into the aquatic environment. The presence of pharmaceutical products, however, is in many cases difficult to detect with existing standard analytical methods.

Additionally, besides this very comprehensive approach to maintaining and improving the overall quality of all waters in Europe, the WFD also has a significant weakness. It lies in the fact that its mechanisms can only be applied if the pressure on the aquatic environment and the related risk has been detected. Regarding pharmaceuticals, this process is currently only beginning. On the other hand, one of the strengths of the WFD is that its most important implementation steps (identifying pressures and impacts on water bodies, design of monitoring programmes, developing river basin management plans) are designed as an iterative process, and new findings can thus be included in the next management cycle. The initial identification of pressures and impacts on water bodies (completed in 2005 according to WFD Article 5) has to be updated by 2013<sup>11</sup> and every 6 years thereafter. PPs can be incorporated into this scheme once more data have become available.

Furthermore, most MS are currently adjusting their monitoring programmes to the main pollutants<sup>12</sup> (e.g. nutrients, heavy metals) and to the requirements set out in the list of priority substances. PPs are mostly not yet on the agenda when designing monitoring programmes. However, in countries like UK and Germany, monitoring of PPs has already taken place to some extent within investigation programmes of the authorities on the occurrence and risk of PPs in the environment. In Germany, three pharmaceutically active substances have even been proposed for inclusion in the WFD monitoring (see sections 3.1 and 3.2 for details).

### ***Drinking Water Directive (DWD)***

The Drinking Water Directive 98/83/EC aims at the protection of human health from harmful influences that might occur through pollution of water intended for human consumption. It also aims at assuring the suitability and purity of water for human consumption. It is strongly linked and synchronised with the WFD. The parameters to be monitored are defined in Article 5 and Annex I of the DWD. It lists 48 parameters (50 for bottled waters) categorised into three distinct groups: microbiological, chemical (meaningful to human health), and indicator parameters (meaningful to supply engineering, aesthetics, and health care).

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<sup>11</sup> Actually, an updated version has to be included in the first river basin management plans already in 2009.

<sup>12</sup> “Main” in terms of amount introduced to the aquatic environment.

No pharmaceutical products are listed in the chemical substances annexes of the Drinking Water Directive. However, some substances used in pharmaceutical manufacturing are included in this list (which also appear in the WFD list of priority substances, see above).

Moreover, the European Commission decided in 2003 not to include endocrine disrupters in the DWD, due to the lack of sensitive detection methods and reliable data concerning their risk to human health in view of their occurrence in water (cf. chapter on endocrine strategy).

However, Member States are free to set values for additional parameters not included in Annex I of the DWD, when necessary for the protection of human health within their national territory or part of it.

In practice, despite the lack of legal requirements to regularly monitor PPs so far, research projects frequently address the issue of PP concentrations in drinking water (e.g. the START-project<sup>13</sup>).

### ***Bathing Water Directive***

The Bathing Water Directive 2006/7/EC is concerned with monitoring and testing bathing water quality in order to protect bathers from health risks and to preserve the environment from pollution. While the old directive introduced in 1976 required regular monitoring of 19 pollutants or other parameters (for instance water colour), the revised directive 2006/7/EC reduces this list to just two microbiological indicators of faecal contamination, *Escherichia Coli* and *Intestinal Enterococci*. This simplification reflects the fact that due to most other water pollution being covered by the WFD, the primary health threat to bathers comes from faecal material (e.g. due to inadequate sewage treatment and pollution due to animal waste). The issue of pharmaceuticals in the aquatic environment will therefore not be dealt with under this Directive.

### ***Groundwater Directive***

The new Groundwater Directive (2006/118/EC) substitutes the old Directive (80/68/EEC). It establishes a regime which sets groundwater quality standards for a minimum list of pollutants (Annex II, Part B of the directive) and introduces measures to prevent or limit inputs of pollutants into groundwater. This Directive was designed to work closely together with the WFD, as it further specifies the WFD's requirements to assess the chemical status of groundwater. Member States have to establish quality standards at the most appropriate level (international, national, river basin districts, or water bodies) by the end of 2008, and in doing so take into account local or regional conditions.

No pharmaceutical products are listed in the Annexes of the Groundwater Directive. However, Member States are required to “*amend the list of threshold values whenever new information on pollutants, groups of pollutants, or indicators of pollution indicates that a threshold value should be set for an additional substance*” (Article 3(6), Groundwater Directive). The directive also includes the requirement to identify and reverse significant increasing trends in pollutant concentrations.

### ***Urban Waste Water Treatment Directive (UWWTD)***

The Urban Waste Water Treatment Directive (UWWTD) (91/271/EEC, amended by Directive 98/15/EC and EC Regulation 1882/2003) concerns the collection, treatment and discharge of urban waste water from urban agglomerations and the treatment and discharge of biodegradable waste water from certain industrial sectors related to the food industry. Its purpose is to stimulate Member States to invest in the collection and treatment of urban waste

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<sup>13</sup> Strategies for tackling Pharmaceuticals in Drinking Water, <http://www.start-project.de/projekt.htm>.

water; the aim is to reduce the input of organic matter and nutrients into European waters according to specific standards and deadlines set out in the Directive (Kemp, 2002). The Directive also encourages the use of sludge whenever appropriate (ICON Consultants, 2001).

The Directive defines three different levels of treatment: primary treatment (by a physical and/or chemical process involving settlement of suspended solids, or other equivalent processes), secondary treatment (involving biological treatment with a secondary settlement) and tertiary treatment (additional treatment of the nitrogen (nitrification-denitrification) and/or phosphorus and/or of any other pollutant affecting the quality or specific use of the water: microbiological pollution, colour, etc). The basic rule for the level of treatment is secondary (i.e. biological) treatment. Treatment has to be more stringent (tertiary with additional nutrient removal) for discharges in so-called sensitive areas (defined according to Annex II of the UWWTD).

The parameters that the UWWTD aims to reduce are only related to organic material and nutrients: it sets minimum standards for the reduction of Biochemical Oxygen Demand (BOD), Chemical Oxygen Demand (COD), total suspended solids, total Nitrogen, and total Phosphorus. Nevertheless, a side-effect of wastewater treatment is that a huge number of other pollutants are also removed from wastewater, in particular many micropollutants such as heavy metals as well as pharmaceuticals. The reduction of the concentration of pharmaceuticals in treated wastewater depends on the particular processes applied, but increases with higher levels of treatment. However, because many pharmaceuticals resist biodegradation (ICON Consultants, 2001), they are frequently found in significant concentrations in sewage sludge.

The UWWTD works with an Emissions Limit Value approach for the parameters it takes into consideration. These parameters (listed above) and their limits are explicitly subject to changes; it is in theory possible that these Emission Limit Values are extended to other parameters, e.g. pharmaceuticals. However, no other contaminants have been taken up in the Directive's annexes in its 17 years of existence. Recently though, there has been significant work on the linkage between the UWWTD and the WFD<sup>14</sup>. In particular the issue of how the treatment plants will respond to the determining of the WFD Environmental Quality Standards has received attention, particularly the influence of the Water Quality Approach on operators used to an Emissions Limit Value approach.

## **2.2.2 Other environmental policies and initiatives**

### ***European Strategy for Soil Protection***

Considering that the status of soil is one of the factors regulating water quality, current European policies for soil protection could also be relevant to the presence of pharmaceutical products in environmental waters.

Different EU policies (e.g. on water, waste, chemicals, industrial pollution prevention, nature protection, pesticides, agriculture) contribute to soil protection. However, as these policies have other aims and other scopes of action, they are not sufficient to ensure an adequate level of protection for all soil in Europe. To address this issue, in 2006 the European Commission

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<sup>14</sup> E.g. the EU-funded project CD4WC – Cost effective development of Urban Wastewater Systems for Water Framework Directive Compliance.



adopted a Communication for a Soil Thematic Strategy<sup>15</sup> and a proposal for a Soil Framework Directive<sup>16</sup>, with the aim of protecting soils across the EU.

The Communication for a Soil Thematic Strategy sets the frame for this regulatory initiative, explaining why further action is needed to ensure a high level of soil protection, setting the overall objective of the Strategy, and explaining what kind of measures must be taken. The proposal for a Framework Directive sets out common principles for protecting soils across the EU, including among others prevention, inventory, and remediation of contaminated soil. With respect to soil contamination, the Directive focuses on dangerous substances, meaning substances or preparations within the Dangerous Substances Directive 67/548/EC and the Dangerous Preparations Directive 1999/45, which do not include pharmaceutical substances. The proposed list of potentially soil polluting activities, however, does include wastewater treatment facilities, which are a source of pharmaceutical substances ending up in water through sewage sludge application on soil.

Although pharmaceutical substances are not part of the current EU policy documents under discussion on soil protection, they have been identified as a priority issue for further research by the working groups set up in preparation of the Soil Strategy. In specific, the Working Group on “Research, Sealing and Cross-cutting Issues” proposed that research should be promoted by DG ENV and DG RES on (Van-Kamp et al., 2004):

- Sampling, identification and quantification of "non-standard" substances (e.g. volatile organic compounds, known and emerging pollutants<sup>17</sup>) in soils.
- Risk evaluation and policy for "emerging" (i.e. up to now not studied) potential pollutants (e.g. human and animal pharmaceuticals, steroids and hormones, personal care products, antiseptics, surfactants, flame retardants, industrial additives and agents, gasoline additives).

### ***Sludge Directive***

Sewage sludge used in agriculture is covered by the Sewage Sludge Directive of 1986 (Directive 86/278/EEC, amended by Directive 91/692/EEC and EC Regulation 807/2003). The Directive’s aim is to “encourage the correct use of sewage sludge” in agriculture, while preventing “harmful effects on soil, vegetation, animals and man”; these effects could be due to the uptake of contaminants in agricultural products.

The restrictions on use of sewage sludge are currently limited to seven heavy metals: cadmium, copper, nickel, lead, zinc, mercury, and chromium. The Directive establishes limits for the concentration of these elements both in soil and in the sludge to be used in agriculture.

The Directive does not make mention of pharmaceuticals in sewage sludge. Because the Directive encourages the application of sewage sludge due to its valuable properties, instead of favouring other forms of disposal such as combustion, it actually encourages at present the spreading of pharmaceuticals and their residues in the environment. Pharmaceuticals in sewage sludge applied to fields can also end up being leached into groundwater, and eventually making their way into surface water and/or drinking water. However, the Directive does foresee a process of its own adaptation to technical and scientific progress, so future

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<sup>15</sup> Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions. Thematic Strategy for Soil Protection. COM(2006) 231. Brussels, 22.9.2006.

<sup>16</sup> Commission of the European Communities. Proposal for a Directive of the European Parliament and of the Council establishing a framework for the protection of soil and amending Directive 2004/35/EC. COM(2006) 232. Brussels, 22.9.2006.

<sup>17</sup> Emerging pollutants typically include pharmaceutical products.

changes to the Directive could in theory address pharmaceuticals. Preoccupation with the issue of pharmaceuticals in the environment, as well as other contaminants, have led some German federal States (*Länder*) to forbid the application of sewage sludge on agricultural fields, making its combustion mandatory.

### ***Endocrine Strategy***

The endocrine system provides the key communication and control link between the nervous system and bodily functions such as reproduction, immunity, metabolism and behaviour. It is composed of three main components: (1) endocrine glands (which secrete hormones), (2) hormones (which circulate around the body via the blood stream and modulate body functions), and (3) receptors (activated by hormones, regulate functions and processes in the tissue). Some chemicals can act on the endocrine system to disturb the mechanisms of the body or to initiate processes at abnormal times in the life cycle. This group of endocrine disrupters comprises natural hormones, natural chemicals, man-made chemicals, and pharmaceuticals.

Several pharmaceuticals are designed to be hormonally highly active, e.g. the contraceptive pill and treatments for hormone-responsive cancers. The residues of such pharmaceuticals enter the aquatic environment via various pathways and may have endocrine disruption effects on humans and wildlife if taken up unintentionally.

The European Endocrine Strategy addresses the potential environmental and health impacts of endocrine disruption in short-term, mid-term, and long-term actions. A key short-term activity was establishing a priority list of substances<sup>18</sup> for further evaluation of their role in endocrine disruption. 553 candidate substances were identified for that list and then further evaluated. Several pharmaceutical substances have been included in this process (e.g. 4-chloro-3-methylphenol and resorcinol, 17 $\alpha$ -ethinyloestradiol), but were found to pose no risk to consumers, including children, from current exposure patterns. There is, therefore, no action at the moment arising from the detection of these substances in the aquatic environment.

However, the identification and evaluation process of relevant substances continues and improves. Any pharmaceuticals detected under the endocrine strategy efforts will be dealt with in existing environmental regulation as far as possible. For the aquatic environment, the endocrine strategy refers to the WFD and its strategy against pollution outlined above (CEC, 2004).

### ***REACH***

Regulation (EC) No. 1907/2006 on the Registration, Evaluation, Authorization and Restriction of Chemicals (the “REACH Regulation”), entered into force on June 1, 2007. It exempts substances “used in” medicinal products from the main provisions on registration, evaluation, authorization, and downstream use of chemicals. It is argued that medicinal products are already regulated within the scope of the Human Use Directive 2001/83, the Veterinary Use Directive 2001/82, and the Regulation 726/2004 (governing the centralized procedure). Some provisions of the Regulation, however, remain applicable, including disclosure of information (on hazardous properties and regarding risk management measures) and restrictions on marketing and use of substances that pose an “unacceptable” health or environmental risk (which will probably rarely be applied to medicinal products) (Bogaert et al., 2007).

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<sup>18</sup> Not to be confused with the list of priority substances under the WFD.

### *IPPC Directive*

Industrial production processes account for a considerable share of the overall pollution in Europe (e.g. emissions of greenhouse gases, wastewater and waste emissions). The IPPC Directive of 1996 (Directive on Integrated Pollution Prevention and Control) provides a set of common rules for permitting and controlling industrial installations in the EU.

In essence, the IPPC Directive is about minimising pollution from various industrial sources. Annex I of the Directive lists industrial installations for which operators are required to obtain an authorisation (environmental permit) from the authorities in the EU countries. About 52.000 installations are covered by the IPPC Directive in the EU.

The IPPC Directive is based on four main principles, namely: (1) an integrated approach, (2) best available techniques, (3) flexibility, and (4) public participation. In the light of PP occurrence in the environment, the first two are of special importance:

- 1) **Integrated approach:** Permits must take into account the whole environmental performance of the plant, including e.g. emissions to air, water and land, generation of waste, prevention of accidents.
- 2) **Best Available Techniques:** The permit conditions (including emission limit values) must be based on Best Available Techniques (BAT) as defined in the IPPC Directive. The Commission issues the so-called BREFs, reference documents on BATs, in order to guarantee a harmonised interpretation throughout the EU.

The list of installations which have to comply with the terms of the Directive (Annex I) include “*Installations using a chemical or biological process for the production of basic pharmaceutical products*”. New installations of this kind have to apply for a permit and have to bring by evidence that emissions to the environment during production are minimal and accord to the BAT.

Furthermore, Annex III lists main polluting substances which should be taken into account for fixing emission limit values. For water, this Annex lists inter alia:

- *substances and preparations which have been proved to possess carcinogenic or mutagenic properties or properties which may affect reproduction in or via the aquatic environment;*
- *persistent hydrocarbons and persistent and bioaccumulable organic toxic substances.*

The proposal for a new directive on industrial emissions<sup>19</sup> refers also to the WFD list of priority substances in this Annex.

With the above requirements, the IPPC Directive ensures that emission of PPs into the environment during their production process is minimised. All in all, there has been much progress in reducing emissions of PPs in the production phase by respecting relevant legislation and by improving the technologies used in industrial manufacturing. Efforts thus to further limit the discharge of PPs into the environment should concentrate on steps beyond (but also prior to) production.

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<sup>19</sup> Proposal for a Directive of the European Parliament and of the Council on industrial emissions (integrated pollution prevention and control) (Recast) [COM(2007) 843 final] [SEC(2007) 1679] [SEC(2007) 1682]

### **3 State-of-play in European countries: Examples of countries on the way to good practice**

In this chapter, three European countries have been selected for presenting their state-of-play on policy approaches regarding the issue of pharmaceutical products in the environment (especially water).

In a recent study focusing on European and North American countries, Doerr-MacEwen and Haight (2006) conclude that government efforts have actually largely ignored management actions related to pharmaceutically active compounds. Efforts of countries have in general been minimal, although some countries have made greater progress than others. Most of the countries' efforts have focused on research and on environmental risk assessment legislation (with the exception of Sweden, see below).

European countries tend to closely follow the regulatory principles and guidance models promoted on an EU level. This chapter takes a closer look at how this is done in practice on a national level and, at the same time, explores other national activities and initiatives complementing EU regulations.

The three countries presented in detail are the UK, Germany and Sweden. The authors feel that these three specific countries merit detailed attention in the present review and can serve as interesting source of information for readers from other countries. In the UK, Sweden and Germany, the presence of PPs in the aquatic environment is an issue of priority and all three countries devote several experts of their authorities (e.g. environment agencies) and scientific institutions to work on the environmental risks of PPs and appropriate management approaches. Sweden has developed a pioneer environmental information and classification scheme for PPs, while UK and Germany seem to concentrate more on research to support further action.

#### **3.1 United Kingdom**

##### **3.1.1 Key competent authorities and policy agenda**

In the UK, the main authorities involved in the authorisation of medicinal products are the Department of Health, the Medicines and Healthcare Products Regulatory Agency, the Health Protection Agency, the Veterinary Medicines Directorate, the Veterinary Residues Committee and the Veterinary Products Committee (ACHS, 2006a).

Other relevant bodies are the Secretariat of the Committee on Toxicity (COT) and the Environment Agency. The UK Drinking Water Inspectorate is involved insofar as residues of pharmaceuticals can become an issue for the quality of drinking water.

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment is an independent scientific committee that provides advice to the Food Standards Agency, the Department of Health, as well as other Government Departments and Agencies on matters concerning the toxicity of chemicals.

The Environment Agency (EA) has no regulatory role in the licensing process of new pharmaceutical products and the related environmental risk assessment. It acts however as advisor to the Veterinary Medicines Directorate and Veterinary Products Committee for issues relating to the environmental safety of veterinary medicines. The EA has no advisory role for human medicine.

The EA has a regulatory role in the manufacturing process (regulations on IPPC sites) and in the disposal of pharmaceuticals (regulatory role concerning especially any emissions to land, air or water from IPPC sites, hospital effluents emitted direct to watercourses, and sewage work effluents). Pharmaceutical manufacturing plants and sewage treatment works are subject to regulation under the UK Environmental Protection Act 1990 and the Water Resources Act 1991. This legislation provides the Environment Agency with the powers to set limits, if deemed appropriate, on the quantities of pharmaceuticals being released into the environment (Environment Agency, 2003).

Although in theory the Water Resources Act would allow the Environment Agency to set limits for the release of pharmaceuticals to surface waters, in practice, this is not implemented. This is due to the fact that these types of pollutants arise from domestic sources and the general public, and water (sewerage) companies would not be able to control the pollution at source. It is also possible for a water sewerage company to impose a limit on the amount discharged to sewers by a manufacturer or formulator and in turn, the EA could set a limit on the amount in effluents released by the water company. However, so far no such pharmaceutical substance-specific limit has been set by the EA (pers.comm. Environment Agency UK, January 2008).

Additionally, some of the pharmaceutical waste falls under the Hazardous Waste Regulations and is thus classified as hazardous waste; under these regulations, cytotoxic and cytostatic medicines are automatically classified as hazardous waste and the EA is currently using a fairly wide definition for cytotoxic and cytostatic; these encompass any medicine that is toxic, mutagenic, toxic for reproduction or carcinogenic. For these, a hazardous waste consignment note must be completed and these are recorded (pers.comm. Environment Agency UK, January 2008).

Next to regulating industry and sewage treatment works, the Environment Agency also has a duty to report on the 'state of the environment' in England and Wales. This involves monitoring and assessing the environment (Environment Agency, 2003). The EA has *monitored pharmaceuticals* both as part of a targeted risk-based programme (Hilton et al., 2003), as well as in a more recent monitoring exercise for the substances fluoxetine and norfluoxetine in 2005 (pers.comm. Environment Agency UK, January 2008).

The EA's position on the issue of pharmaceuticals in the environment was set out in its relevant Statement published in 2003 (Environment Agency, 2003).

In the ongoing implementation of the EU WFD, there are at present no pharmaceuticals on the list of *UK-specific chemicals for the WFD* (UK Technical Advisory Group on the Water Framework Directive, 2007). The relevant report, which contains the list of substances identified so far for WFD Annex VIII in the UK, is currently being updated following consultation. However, the prioritisation to identify Annex VIII substances is an on-going process, with the possibility of further substances being added (and their corresponding standards for environmental quality proposed). The process uses criteria on occurrence, persistence, toxicity and bioaccumulation in order to identify new substances. Oestradiol and ethinyl oestradiol have both been identified by the EA as *potential* UK specific pollutants. Work is currently underway to investigate whether PNECs (predicted no effect concentrations) can be developed for these substances. Based on the outcomes of this work and peer reviews, these substances may or may not become UK specific pollutants (pers.comm. Environment Agency UK, January 2008).

The EA also argues that there is sufficient evidence of harm to fish that a risk management strategy is required for *synthetic and natural oestrogens* entering the environment via sewage effluent. The EA therefore encourages the water industry to investigate treatment technologies



aimed at minimising any oestrogenic impacts of sewage effluent. EA research and research of others suggest that, in typical circumstances, levels of other pharmaceuticals entering rivers are not high enough to cause immediate harm to aquatic life (i.e. levels which will result in death). However, there is insufficient information available to determine whether exposure to low levels of these substances over long periods of time is having an impact (Environment Agency, 2003). Indeed, the *possible environmental effects of low level continuous aquatic exposure to human pharmaceuticals* have been a key issue of concern for the Environment Agency. The Agency therefore called in 2003 for the development and implementation of chronic toxicity testing procedures using aquatic organisms. As a result, chronic aquatic toxicity tests have been adopted in the most recent environmental risk assessment guidance document for human pharmaceuticals produced by the European Medicines Agency (EMA) in support of Directive 2001/83/EC (Crane & Watts, 2006).

In 2006, the Environment Agency also organised a multi-stakeholder workshop on the issue of chronic aquatic ecotoxicity testing of human pharmaceuticals. The workshop gathered together pharmacology, ecotoxicology and chemistry experts from the industrial, research and regulatory sectors to establish a consensus on how and when to assess chronic impact through low-level exposure of pharmaceuticals in the aquatic environment. The workshop recommended that a chronic impact decision tree should be created to assist in the development of an effective and efficient testing strategy. Increased collaboration and data-sharing between both the research-based and the generic pharmaceutical industries and regulators should be encouraged, while the formation of a joint task force should be considered (Environment Agency, 2006).

In the UK, there are currently approximately 3000 pharmaceuticals licensed for human use. The vast majority of these are licensed using EU legislation on medicine authorisation (see Chapter 2). The responsibility for issuing licences for new pharmaceutical products and for the related environmental risk assessment lies with the Medicines and Healthcare products Regulatory Agency (MHRA), part of the Department of Health (Environment Agency 2003). As elsewhere in Europe, ERA for all new marketing authorisations of human medicine is currently conducted in accordance with the 2006 EMA guideline. At present, there seems to be no plan in the UK to examine human medicine authorised prior to the ERA regulatory regime ("old medicine"). However, those products authorised since 1995 (when the first draft EMA guideline was issued) will have had some form of ERA conducted (pers.comm. Medicines and Healthcare products Regulatory Agency and Environment Agency UK, January 2008).

The EA has in recent years conducted two *prioritisation exercises*, which used a simplified PEC/PNEC approach, in order to rank pharmaceuticals based on their relative risk to the aquatic environment (Environment Agency, 2006b) and a second scheme is to be published in 2008. These schemes investigated the top 300 pharmaceutical substances used in the UK (by volume) and also included "old" generic substances. However, these exercises only identified substances for further investigation and were not part of a formal ERA process. They therefore suffered significant limitations due to the lack of experimental data on the ecotoxicity and fate in sewage treatment and in the environment for the majority of active substances (pers.comm. Environment Agency UK, January 2008).

As far as veterinary medicines are concerned, the responsibility for evaluating their dossiers and issuing licenses in the UK lies with the Veterinary Medicines Directorate (VMD). The environmental risk assessment of veterinary medicines has been a requirement for all new product applications since 1992 (according to EU regulations) (ACHS, 2006a). The VMD gives high priority to the issue of veterinary medicine in the environment, being among the

first agencies to appoint a specialist for assessing the environmental safety section of the authorisation dossiers (pers.comm. VMD and Environment Agency UK, January 2008).

### 3.1.2 Take-back scheme

In 2005, the UK passed legislation amending the 1992 National Health Service Regulations (S.I. 2002/662) to govern the provision of pharmaceutical services. According to these regulations, “[a] pharmacist shall ... accept and dispose of unwanted drugs presented to him for disposal” (United Kingdom, 2005: Schedule 1, Part II, Art. 12). Pharmacies thus have to take back and sort unwanted and/or unused medicines brought back by patients and return these to the National Health Service (NHS). The collection is not financed nor organised by the pharmaceutical industry, but by local health authorities. Returned medicines are incinerated.

According to a study by the National Health Service published in 2006 (NHS Health and Social Care Information Centre, 2006), all Local Health Boards (LHBs, in Wales) and Primary Care Trusts (PCTs, in England) had a scheme in 2004-05 for the collection and disposal of unwanted medicines through pharmacies. The NHS collected detailed information on the weight of unused and unwanted medicines taken back by 252 of the PCTs. However, no information is made available on the estimated relation between drugs sold, the ratio of these drugs that are potentially unused, and the rate of unused drugs taken back to the pharmacy. To have an idea of the effectiveness of the scheme, one needs to know what happened to the drugs after they were prescribed and purchased. The drugs may be consumed, be left unused in people’s home, disposed of via the toilet or bin, or taken back to pharmacies. Effectiveness is not only a function of the amount of drugs recovered but also the proportion of the total *actual* waste stream this amount represents. New research commissioned by the Department of Health (to be undertaken in 2008-2009) will aim to establish the amount of medicines "wasted" and the complex and varied reasons why people do not take the medicines prescribed for them (pers.comm. Department of Health and Environment Agency UK, January 2008).

### 3.1.3 Activities supportive of policy

The UK stands out for its extensive research activities to support better understanding and better implementation of regulations relevant to the discharge of pharmaceutical products into the environment. The issue of pharmaceuticals in the environment is also discussed in an open manner within multi-stakeholder committees including both governmental and industry representatives (see below information on the activities of the UK Advisory Committee on Hazardous Substances).

#### 3.1.3.1 Research activities

The presence of pharmaceuticals in the environment has been an issue of concern for the Environment Agency for several years. In consequence, the Agency initiated relevant and in-depth research on this subject, some of which was already highlighted above.

In 2000, the Agency completed a review of the information available in scientific literature on human PPs in the environment (Environment Agency, 2000).

As a consequence of the review findings, a second stage of work was conducted, implementing a targeted monitoring programme for PPs in the aquatic environment (reference to this targeted risk-based programme was already made above). This work was completed in 2003 and described a screening process that the Agency adopted to allow PPs to be ranked,

based on their relative risk to the aquatic environment. It also described a short targeted monitoring programme that was conducted for a number of the higher priority PPs in England and Wales (Environment Agency, 2006). As mentioned above, this study showed that none of the PPs were found at levels which were high enough to cause acute toxic effects to aquatic organisms, and that insufficient data was available to assess more subtle long-term effects on aquatic organisms (e.g. effects on growth, ability to reproduce) (Environment Agency, 2006). In addition, the occurrence data generated by this targeted monitoring will be used to verify the Predicted Environmental Concentrations (PECs) derived during the screening process (based on the EU Guidance Document on risk assessment), to reduce the uncertainty associated with the screening process, and to provide actual data to enable the Environment Agency to better determine potential risk (Environment Agency, 2003). In 2005, the Agency updated the screening process with new data and obtained a list of priority substances. The list is being refined in collaboration with industry (ACHS, 2006).

As concerns veterinary medicine, the Environment Agency followed a similar approach to that for human pharmaceuticals. This approach resulted in the publication of a Review of Veterinary Medicines in the Environment (Environment Agency, 2002) and a subsequent Targeted Monitoring Study for Veterinary Medicines (Environment Agency 2006b) (ACHS, 2006a). In addition, the Veterinary Medicines Directorate has commissioned specialised research projects on the ecological effects of sealice treatment agents, the assessment and management of inputs of veterinary medicines from the farmyard as well as on the environmental exposure to cypermethrin released to the farmyard (ACHS, 2006a).

As concerns the future agenda of key issues to be checked, the Environment Agency points out that most important knowledge gaps include the lack of data on chronic effects, the lack of data on fate and behaviour, and the issue of mixtures of substances with the same mode of action (specifically in relation to assessing potential environmental impacts) (ACHS, 2006b).

### 3.1.3.2 Pharmaceuticals on the agenda of the UK Advisory Committee on Hazardous Substances

The Advisory Committee on Hazardous Substances (ACHS) provides expert advice on the science behind hazardous chemicals in the UK.<sup>20</sup> It meets to discuss, among others, further research and action needs. In 2006, the ACHS conducted a horizon scanning exercise to identify whether new issues within its remit are likely to emerge for which scientific advice or research might be needed, and to review and provide advice on such issues. In this context, the ACHS considered that especially the effects of pharmaceuticals in the environment should be discussed further (ACHS, 2006c). The Committee was informed of important relevant research activities carried out by the Environment Agency, but also of relevant programmes of the pharmaceutical industry. The ACHS acknowledges projects underway to assess the risks of pharmaceuticals to the environment and shall revisit this subject once these projects make more progress (ACHS, 2006c).

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<sup>20</sup> The Advisory Committee on Hazardous Substances (ACHS) is made up of eleven scientists, drawn from both private-sector industries and public-sector non-governmental organisations and a lay member. The Committee Secretariat is based at DEFRA. The respective fields of Committee members include medicine, chemistry, ecotoxicology and other fields of science that provide a valuable contribution to the successful risk management of chemicals. The ACHS is politically independent, and provides objective, impartial advice from a purely scientific perspective. In April 2001, the ACHS adopted the principal role of advising the UK Chemicals Stakeholder Forum. In particular, the Committee has advised the Forum on its criteria for concern, in light of physical and chemical properties of substances. The Committee has retained its role of advising the government directly where appropriate, and has recently provided advice in areas such as the toxicity to non-target wildfowl arising from ingestion of lead shot used in game shooting (DEFRA, 2007).



## 3.2 Germany

In Germany, the framework for the issue of pharmaceuticals in the environment is mainly limited to the transposition of European directives into national law. In addition, though, various other efforts have been undertaken or are being carried out. This case study will address in brief a) relevant regulations, and b) other policy-supportive activities; this last point includes official initiatives related to the subject (e.g. conferences, dialogue efforts, official positions regarding problem areas), as well as monitoring and research efforts.

### 3.2.1 Relevant regulations

#### 3.2.1.1 Pharmaceutical regulations relating to the environment

The EU requirements concerning environmental risk assessments of pharmaceuticals were first transposed into German law in 1996 with the 6<sup>th</sup> amendment of the Pharmaceutical Act (*Arzneimittelgesetz*), and then included in the 1998 revised version of the act. It requires the evaluation of the environmental risk resulting from a new substance applying for authorisation, in the case of both human and veterinary pharmaceuticals. If an environmental risk is identified, the authorisation of the pharmaceutical will be linked to certain obligations and conditions. The competent authority on the federal level (the *Bundesinstitut für Arzneimittel und Medizinprodukte* in the case of human pharmaceuticals, and the *Bundesamt für Verbraucherschutz und Lebensmittelsicherheit* in the case of veterinary products) determines these, together with the Federal Environment Agency.

The Federal Environment Agency is the organisation responsible for carrying out the environmental risk evaluation of human and veterinary pharmaceutical products. The agency started evaluating veterinary products in 1998, and since 2003 also evaluates human pharmaceuticals. Regarding veterinary products, the Agency has been successful in a significant number of cases in combining the authorisation with practicable risk mitigation measures that reduce the products' environmental impacts. In the field of human pharmaceuticals, however, where in theory risk mitigation measures (which cannot curtail the authorization) can also be applied, the Agency sees the need for further efforts. The Agency's overall view of German implementation of EU regulations is very positive: the Agency has exhausted the possibilities within the framework provided by the EU regulations (Presentation Holzmann, Presentation Schlimm, both in German Federal Environment Agency, 2005).

Risk mitigation measures for veterinary products have up to now primarily aimed at reducing environmental exposure, for instance by reducing the direct access to surface water of cattle treated with the veterinary product. Other examples are product use instructions regarding the application of dung, warning notices in the package insert or specific requirements concerning the packaging, such as a specific form or closure system (Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen, 2007: 209).

At the *Länder* level, some states (e.g. Bavaria and Nordrhein-Westphalen) have recently passed legislation that restricts the use of sewage sludge in agriculture. The presence of pharmaceuticals in sewage sludge, and as consequence the possibility of them entering environmental waters, was one of the reasons for passing this decision.

#### 3.2.1.2 Implementation of regulations concerning pharmaceutical take-back schemes

The European regulations requiring the set up recovery systems for unused pharmaceuticals, which entered into force in 2005, did not have to be implemented from scratch in Germany, because such schemes were already in place.

In Germany, old unused medicines are legally classified as residual waste and can be disposed of with regular house waste. House waste is divided into different categories: of relevance for this case are packaging waste as well as residual house waste. Due to the universal acceptance of the packaging recycling system in Germany (known as “Green Dot”), a significant amount of the pharmaceutical companies work with this system to guarantee the recycling of its packaging (which they are bound to under German waste regulations).

On the other hand, two companies operate drug take-back systems at pharmacies: Vfw-Remedica and MEDIrecycling. Both collect unused medicines from pharmacists, sort and recycle the packaging (thus also covering pharmaceutical companies’ requirements regarding packaging), and incinerate the unused pharmaceuticals. Vfw-Remedica, the largest of both, covers about 16,000 of the 21,000 German pharmacists as well as 2,000 hospitals and further health facilities (MEDIrecycling takes back medicine from only a few thousand pharmacies).

Some studies have analysed the relative importance of both disposal systems for pharmaceuticals. Innovations Report (2002) states that 86% of the 1.6 billion medication packaging disposed yearly is documented in private households (and partly disposed via the Green Dot (*Grüner Punkt*) household recycling system). Only 14% is returned to the pharmacies. A survey showed that 95% of the respondents know the “Green Dot” sign for packaging recycling but only 3% are familiar with the Vfw-Remedica system for pharmaceutical products. Additionally, only few pharmacies offer easily accessible collecting boxes while relevant instruction signs are missing in 9 out of 10 cases.

Other studies have also concluded that consumers, used to disposing product packaging in the “Green Dot” containers, do not usually know of the existence of take-back schemes at pharmacies. The tendency is thus to eliminate the surplus content of the packaging (e.g. via the toilet or house waste), as done with other packaging, and to dispose it in these waste containers. Alternately, the packaging is disposed of with its unused contents inside. The analysis of water leachate of landfills carried out in certain German regions, in fact, showed very high values for pharmaceutical compounds in leachate waters (BLAC, 2003).

The experience gained in Germany shows clearly how previous legislation related to take-back and recycling of pharmaceutical products and their packaging (in this case regulations regarding product packaging), in combination with an inadequate consumer information, can partly work against new schemes and measures aimed at reducing the impact of unused pharmaceuticals on the environment. In spite of the very high acceptance of Vfw-Remedica among pharmaceutical companies and pharmacies, the take-back scheme is not overly successful, particularly when compared with the amount of pharmaceutical waste which is discarded in “Green Dot” waste containers. Another point to bear in mind is that, under this model, the setting-up of a new take-back scheme for pharmaceuticals goes against the economic interests of the predominant, general packaging recollection scheme (in this case “Green Dot”), because it implies a reduction of its packaging market or of its market share.

### **3.2.2 Activities supportive of policy**

A significant amount of non-regulatory activities related to the issue of pharmaceuticals in the environment have been implemented by German authorities and institutions. This chapter analyses the position of relevant authorities vis-à-vis the issue (i.e. position on the political agenda, possibilities for future action, outreach efforts), the research being undertaken, and the monitoring approaches.

### 3.2.2.1 Official initiatives

The issue of pharmaceuticals in the environment has been gaining profile in German public opinion in the last couple of years; there are also signs that it is climbing on the political agenda. In May 2007, the German Council of Environmental Advisors published an extensive position paper on the subject (SRU, 2007). This Council is a highly prestigious independent scientific advisory committee for the German federal government, which directly links to the Environment Minister. Also in 2007, the parliamentary group of the Green party used the instrument of information request (a “small inquiry”) from the government on the subject of pharmaceuticals in wastewater/sewage sludge and related government initiatives (Deutscher Bundestag, 2007a), to which the government was obliged to give detailed answers (Deutscher Bundestag, 2007b). Up to 2007, there was no joint work between pharmaceutical companies and government bodies to reduce the input of pharmaceuticals into the environment; however, a “dialogue process” on “green pharmacy” has been initiated (Deutscher Bundestag, 2007b).

At the technical level, among other things, very significant expertise has been developed on this issue within the Federal Environment Agency (also in charge of the environmental risk assessments for pharmaceuticals, see previous chapter). The Agency sees in very critical light the current knowledge gaps in the issue, which in its opinion complicate the development of additional regulatory efforts (Koschorreck, pers. comm.).

One of the most important of these knowledge gaps, in the opinion of the Agency, is given by the issue of pharmaceutical products authorised *before* the new European regulations (on environmental risk assessment) came into force. The Agency sees a major gap in the product-authorisation regulations due to their failing to address the issue of environmental risk assessments of previously authorised pharmaceuticals, which do not have to comply with the new requirements. The agency’s argument for a programme to address the environmental evaluation of previously authorised veterinary and human pharmaceuticals is backed up with an analysis of the regulatory processes for other groups of chemicals. In the context of various waves of European regulations that addressed the requirements (including environmental ones) for certain groups of substances, the issue of “old” compounds was addressed (e.g. pesticides, food additives, biocides, and chemicals). The Agency’s position is that this issue has to be addressed and that it will continue to advocate for it. Nevertheless, up to the present the Agency’s efforts to target this information gap have not passed early design and planning stages (Koschorreck, pers. comm.). The Agency has also urged pharmaceutical companies developing new products to address this issue, because of the competitive disadvantage for new products that the differentiation between previously authorized (no ERA submitted) and currently authorized (ERA submitted) implies (Holzmann, 2005; Schlimm, 2005).

The knowledge gap concerning the environmental behavior of previously authorized pharmaceuticals is also highlighted in the position paper of the German Council of Environmental Advisors. This paper further emphasizes the need for more detailed figures regarding the use of pharmaceuticals, currently only available in highly aggregated forms. The system to compile this information should be established with the cooperation of industry (SRU, 2007).

Regarding risk management, the Agency sees extremely limited possibilities for management measures at product level; these would be limited to e.g. take-back schemes and extra packaging for the disposal of estrogen patches (Presentation Rönnefahrt, 2007). Most possibilities lie outside of this legal framework, and would include options such as risk communication (“green labelling”), improved treatment processes in wastewater treatment plants, avoiding the fertilisation of fields with sewage sludge, etc.

The recommendations of the German Council of Environmental Advisors in the area of risk management also refer to actions such as the phasing out of the use of sewage sludge as agricultural fertilizer or the possibility for better labeling on pharmaceuticals and better doctor, prescriber, and consumer information, with the aim of reducing the disposal of unused pharmaceuticals in toilets and increasing the amount of pharmaceuticals returned at pharmacies (SRU, 2007).

In the field of outreach, the German Federal Environment Agency organised a major conference on the subject in September 2005. A considerable amount of university-organised conferences on the subject or on an overarching subjects (e.g. micropollutants in general) have been held.

### 3.2.2.2 Research activities

Germany has seen major research efforts related to pharmaceutical compounds in water, and efforts continue both at federal and state level. Significant capacity and expertise have been generated, both in government agencies, universities, and other institutions, including private companies. In the following, the most important research activities within Germany will be presented, along with their possible relevance for policy.

After the first findings of pharmaceuticals in environmental waters, which were covered extensively in the press, a large-scale study was commissioned by the environmental ministers of the German *Länder*, which a) compiled previous research and monitoring efforts related to pharmaceuticals in waters, and b) co-ordinated a national study to analyse the presence of pharmaceuticals. The *Federal and States' Committee for the Safety of Chemicals* (BLAC) study came out in November 2003, presented the monitoring results (carried out for sewage waters, surface waters, groundwaters and for waters infiltrated through landfills) and their analysis. On this basis, suggestions for improving the monitoring and information base in the future, as well as some preliminary recommendations on how to reduce the entrance of pharmaceutical products into the environment, were presented. The study highlighted, for instance, the need for figures for the consumption of the different pharmaceutical products on the part of official sources (currently the industry has these figures, but is not required to share them). The value of the study, though, is given by the thorough diagnosis of the current situation in Germany, and its implications for monitoring plans.

A current German-funded large-scale research project is called “Management Strategies for Pharmaceuticals in Drinking Water” (German acronym: START; [www.start-project.de](http://www.start-project.de)). The project has its focus on relevant social actors and their behaviours, analyzing for instance the possibility of changing consumer and prescriber behaviour, changing the ways and amounts in which pharmaceutical products are expended, etc. It differentiates between three action fields for addressing this problem: technical level, actor-behaviour level, and the active compounds and green pharmacy level. The project results should be particularly interesting for policy initiatives aiming to address actor behavior.

Furthermore, a variety of research projects focus on the behavior of pharmaceuticals in specific sections of the water cycle, closing particular information gaps regarding processes in e.g. riverbeds and sediments.<sup>21</sup> Other research projects focus on water treatment

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<sup>21</sup> A major study analysed the behaviour of pharmaceuticals in water when being filtrated through river banks and sediments (called NASRI – Natural and Artificial Systems for Recharge and Infiltration; consortium of universities, public works, and government departments). A study that is currently in its early stages analyses the natural breakdown processes of pharmaceuticals in rivers and their sediments (University of Bayreuth).

technologies<sup>22</sup> as well as on the biological and ecotoxicological effects of pharmaceuticals in environmental waters.

### 3.2.2.3 Monitoring activities

In 2003, the results of the large-scale monitoring study of the *Federal and States' Committee for the Safety of Chemicals* (BLAC) were presented, which among other things carried out an evaluation of the occurrence of pharmaceuticals in the country (see previous section). After this study, and because water monitoring falls under the attributions of the individual *Länder*, the monitoring for pharmaceuticals has been less uniform. Several *Länder* have carried out their own literature studies and reviews: Baden-Württemberg completed a review of the occurrence of pharmaceutical products in its waters (in the year 2002); Nordrhein-Westfalen recently conducted a literature study of the occurrence of pharmaceuticals in the environment (in 2007). The monitoring of the Rhine, which crosses several different *Länder*, includes permanent monitoring for pharmaceuticals (Koschorreck, pers. comm.).

There are efforts to include some active pharmaceutical compounds under the monitoring of the Water Framework Directive (WFD). The position paper of the German Council of Environmental Advisors also explicitly recommends including some pharmaceuticals in the list of WFD priority hazardous substances and to aim for the setting of environmental standards for them (SRU, 2007). Three pharmaceutically active substances have been proposed for inclusion in WFD monitoring in Germany: Diclofenac, Carbamazepin, and Ibuprofen (Koschorreck, pers. comm.).

## 3.3 Sweden

As is the case of Germany and UK, Swedish regulations of relevance for pharmaceuticals in the environment are limited to the national implementation of the European product-authorisation regulations presented in Chapter 2. A more innovative side to the country's treatment of pharmaceuticals is its widely-known environmental information and classification scheme of pharmaceuticals, in which industry, government and other stakeholders participate.

This case study will present in brief a) relevant regulations, b) the Swedish voluntary environmental information and classification scheme, and c) other relevant initiatives supporting the presence of PPs on the environmental policy agenda. Especially, the Swedish voluntary scheme is the end-result of a complex process, which was initiated in its first form by the Swedish government, when analysing the possibility of introducing regulations addressing pharmaceuticals in the environment. Due to the importance of the system's development for the final result, the section on the classification scheme will also cover the history of its development.

### 3.3.1 Relevant regulations

#### 3.3.1.1 Regulatory context

Swedish regulations concerning the input of PPs into the environment mainly reflect the implementation of European product-authorisation directives and guidelines; Swedish medicinal legislation is essentially the same as that of the rest of the EU. The Swedish government transposes EU Directives into acts and ordinances; the Swedish Medical Products

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<sup>22</sup> An example is a project which developed a procedure for separating and treating hospital water before it reaches city treatment plants (Fraunhofer UMSICHT and IUTA).



Agency (MPA) transposes these into provisions, which are published in the MPA's own Code of Statutes. The authority of the MPA to issue regulations is primarily laid down in the Medicinal Products Act and the Medicinal Products Ordinance. The MPA is the body in charge of the authorisation of both human and veterinary drugs.<sup>23</sup>

Only those medicinal products that count with a marketing authorisation, either issued by the Swedish Medical Products Agency (national authorisation) or granted for the entire European Community (a Community authorisation) may be placed on the Swedish market.<sup>24</sup>

The EU revision of the pharmaceutical legislation of 2004 involved changes to 3 EU directives. Some of the changes were already implemented in Swedish legislation; the rest was implemented into Swedish national legislation on May 1, 2006. One of the changes in EU legislation that did not have to be implemented in Sweden because of its previous existence is the country's take-back scheme. This highly-developed scheme, which is also widely known among the public, will be presented in the following section.

### 3.3.1.2 Pharmaceutical take-back scheme

As in the case of Germany, the European regulations requiring the set up of recovery systems for unused pharmaceuticals, which entered into force in 2005, did not have to be implemented in Sweden from scratch, because such a scheme was already in place.

The Swedish take-back scheme is strongly determined by the structure of its healthcare system. All pharmacies in Sweden belong to the state-owned corporation Apoteket (National Corporation of Swedish Pharmacies), which provides this company with significant powers in its dealing with other stakeholders.<sup>25</sup> Apoteket runs a pharmaceutical take-back scheme (since the 1990s), in which consumers can return their unused or expired medication to any of the chain's pharmacies. These pharmaceuticals are then collected and incinerated in approved incineration plants.

There is a high level of awareness of Apoteket's take-back scheme among the Swedish public. Apoteket claimed in 2004 that approximately 65% of the Swedish public disposed their unused medications by returning them at pharmacies, whereas in 2006 the figure had increased to 73%. In the year 2006, the amount of pharmaceuticals returned increased by 4% compared to the previous year (Apoteket, 2006a).

Apoteket has invested significant efforts in increasing the available information on the environmental risks of drugs, and in increasing the public's awareness of the environmental consequences of their disposal. Among the latter are campaigns that address the public's behaviour regarding surplus or leftover drugs (e.g. through advertising news about the monitoring results of the County Councils on the presence of PPs in drinking water in the press, via relevant information on posters and small take-away brochures at each pharmacy counter).

Other approaches used by Apoteket and others for reducing the environmental impact of pharmaceuticals include reducing the amount of unused medicine, e.g. through the use of smaller than usual "starter packs". These reduce the amount of leftover medicine in the case of treatment being interrupted (Stockholm County Council, 2007).

<sup>23</sup> [http://www.lakemedelsverket.se/Tpl/NormalPage\\_1003.aspx](http://www.lakemedelsverket.se/Tpl/NormalPage_1003.aspx).

<sup>24</sup> [http://www.lakemedelsverket.se/Tpl/NormalPage\\_2173.aspx](http://www.lakemedelsverket.se/Tpl/NormalPage_2173.aspx).

<sup>25</sup> This retailing monopoly will be broken up and by January 2009 new companies should be permitted to enter the business, according to the promises of the recently elected government.

Although the Swedish take-back scheme is clearly highly successful, there are no figures yet that quantify reliably the total amount or the percentage of dispensed medicines that are returned to pharmacies. Apoteket bases its positive evaluation on the high percentage of the public that claim to know of and use the take-back scheme. Nevertheless, the proportion of unused medication that is in fact returned may not be as high.

Other indirect estimates of the proportion of unused medications that are returned to pharmacies do not give values as optimistic as those of Apoteket. According to studies cited in Ekedahl (2006), the proportion of dispensed medicines returned to Swedish pharmacies ranges between 2,3% and 4,6% of the total volume dispensed (studies published in 1999 and 2003). On the other hand, estimates for the total amount of pharmaceuticals that go unused (i.e. unused pharmaceuticals returned + unused pharmaceuticals not returned) are extremely variable. In the Swedish book “Environment and Pharmaceuticals”, the proportion of drugs which never get used is placed at “about 5 per cent” (Apoteket, 2006), whereas a study in France estimated that on average one out of two prescribed medications is not consumed (i.e. ca. 50% of the medicine sold goes unused) (Grass & Lalande, 2005).

### **3.3.2 The Swedish pharmaceutical classification scheme**

The current voluntary classification system for pharmaceuticals is a result of early regulatory efforts on the side of the Swedish government, as well as of public concern, political will and pressure, and the structure of the Swedish health system. So as to understand the voluntary classification system implemented in Sweden (the result of a complex political process), as well as its consequences, the developments leading to it will be summarised briefly.

#### **3.3.2.1 Historical background**

As a reaction to a series of high-profile cases of findings of pharmaceutical residues in waters, including in the water supply, the Swedish government commissioned a report on the subject from the Swedish Medical Products Agency (MPA) (Mattson et al., 2007). This report, as well as addressing the environmental effects of pharmaceuticals, cosmetics and hygiene products, “was also to submit proposals on measures to reduce environmental effects of the products [...]. A study of the possibilities to introduce environmental classification of pharmaceutical products was also part of the commission” (MPA, 2004). Regarding this latter point, the possibility of this environmental classification scheme infringing against European regulations was a crucial issue to be analysed.

The MPA report was published in August 2004. The report’s authors highlighted the major knowledge gaps in the subject, and as a consequence considered it too early to take measures such as implementing an environmental classification scheme of pharmaceuticals. It concluded that (MPA, 2004):

- “Regulation of pharmaceutical products is largely based on EU directives. Considering current legislation, environmental protection interests, and the internal market, the most suitable approach is to work actively at the EU level for a discussion of environmental classification of pharmaceutical products. Developing a common European environmental classification system is preferable to having different regional systems being developed separately.”
- “EU legislation places requirements for submitting data and hindrances for a number of classification models. A Swedish national environmental classification, based on environmental risk assessments included in marketing applications, cannot be regarded as being in conflict with the legislation.”

- “While awaiting a possible European system of environmental classification, a voluntary national system might be introduced. The lack of scientific data will, however, lead to practical problems and a risk of arriving at erroneous conclusions is apparent. Thus, the Medical Products Agency is of the opinion that the benefit of a national system is doubtful.”
- “If a voluntary Swedish classification system is introduced, the responsibility for obtaining and providing the necessary data should lie with the pharmaceutical industry. A voluntary classification system should rely on self regulation by the pharmaceutical industry as civic governance could be perceived as indirect regulation skewing competitiveness. The review of published environmental information should be the responsibility of the Medical Products Agency.”

The reaction to the report from the press and environmental groups was negative: the report was considered “bland” and was deemed to have no relevant or practical suggestions as to how the problem should be addressed. In its aftermath, the Minister for Environmental Affairs called a meeting with stakeholders and, in the words of the Swedish pharmaceutical industry, “made it very clear that she expected rapid action on developing an environmental classification scheme, and if EU laws prohibited a mandatory classification system then such a system should be on a voluntary basis” (Mattson et al., 2007).

Sweden’s pharmaceutical industry agreed to the implementation of such a system. This was also the result of the fact that in 2003 Stockholm City Council and Apoteket had launched a classification scheme of their own, and that the pharmaceutical industry was not happy with some of the characteristics of this other system. It was viewed as more productive to become part of the process and influence it, than try to argue against a classification system set up by others (Mattson et al., 2007). The fact that the public health bodies could eventually decide to use this system as a criterion in its tenders for buying pharmaceuticals was also relevant. This early scheme and the changes it underwent when the industry and other stakeholders took up the issue are presented in the following section.

### 3.3.2.2 The voluntary classification scheme and its evolution

The classification scheme in its first form was developed by the Stockholm City Council and Apoteket. As a result of the developments described in the previous section, the industry, the Stockholm City Council, Apoteket and others jointly developed another system. Both systems are presented in the following.

The Stockholm City Council is the organisation responsible for providing public healthcare for the people of the region. It defined the issue of pharmaceutical residues in environmental waters as one of its key environmental issues; its approach was based on three different pillars (Wennmalm, 2004):

- To influence processes of pharmaceutical legislation
- To establish environmental classification of pharmaceuticals
- To analyse pharmaceutical residues in surface water

In the year 2003, working in conjunction with Apoteket (the National Corporation of Swedish Pharmacies, a state monopoly in charge of all pharmacies), the council launched an environmental classification system for pharmaceuticals. This system is based on the *hazard* of the pharmaceutically active ingredient, i.e. on its inherent ability to affect the environment. The active ingredients targeted by the system are mainly included in human PPs, while the system considers both prescription and over-the-counter drugs. (This is also the basis for other



classification schemes, such as that of chemical compounds under the new REACH legislation. On the other hand, the environmental *risk* assessment for pharmaceutical products also takes into consideration the (usually estimated) concentration of the pharmaceutical product in the environment, in view of its possible or actual consumption). The classification system came to be known as the “*Stockholm model*”. Box 1 presents the main characteristics of the scheme.

### Box 1 The “Stockholm model”

The “Stockholm model” focuses on the environmental *hazard* of a pharmaceutical product, i.e. on its inherent ability to affect the environment. Due to the lack of official standards, a working model was developed, based on biodegradability (i.e. related to *persistence* in the environment), potential for *bioaccumulation*, and *toxicity* to aquatic organisms (called “PBT assessment”). Every factor is valued from 0 to 3 and the results are added up; the best total possible score from an environmental perspective is 0, with the highest score being 9. The evaluation is based on data provided by the manufacturers. Every year, the evaluation of new active substances is made public (around 50 substances were added to the list in 2007).

Due to developments in the Swedish public awareness of the environmental presence of PPs as well as the existence and implementation of the “Stockholm model”, the industry was willing to collaborate in the creation of a new classification scheme with other stakeholders. The stakeholders who collaborated on this second classification scheme, which came to be known as the “Swedish model”, included LIF (Swedish Association of the Pharmaceutical Industry), Stockholm County Council, Apoteket, the Swedish Association of Local Authorities and Regions (SKL), and the MPA (Medical Products Agency). In parallel with the Swedish task force, LIF also put together an international task force with environmental expertise from several pharmaceutical companies, i.e. Pfizer, AstraZeneca, Merck, GSK, Lilly and Roche. A reference group was also formed, with stakeholders from the academies, governmental agencies, and representatives of patients and physicians (Mattson et al. (2007)). The resulting system is summarised in the following Box 2.

### Box 2 The “Swedish model”

A major difference regarding the original Stockholm model is that, in the Swedish model, the evaluation of active substances is not only based on the environmental hazard of the product (its inherent ability to affect the environment), but also the associated risk, i.e. an assessment of the *probability* that adverse effects will occur and of their possible extent, based on the current use of the pharmaceutical product (Apoteket, 2006; Stockholm City Council, 2007).

The environmental hazard and risk assessment is carried out by the Swedish Association of the Pharmaceutical Industry (Stockholm City Council, 2007). The assessment is compliant with the European EMEA guideline for risk assessment of pharmaceuticals and has the PEC/PNEC concept at its centre. In fact, for newly authorised substances, the data published in the Swedish classification system are based on the ERA studies submitted and approved by the Swedish MPA. The lengthy (and confidential) information in the ERA studies is processed and condensed into more simplified information made available for public use. A difference to the risk assessment under the EMEA guideline is that the Swedish classification system does not follow a tiered approach.

Additionally, the information on risk & hazard is presented for three target groups: patients, prescribers, and specialists (scientists, experts etc.).

At the *patient level*, and based on the PEC/PNEC ratio outlined above, a verbal message is provided for the patient’s information:

PEC/PNEC < 0.1	“Use of the medicine has been considered to result in insignificant environmental risk.”
0.1 < PEC/PNEC < 1	“Use of the medicine has been considered to result in low environmental risk.”
1 < PEC/PNEC < 10	“Use of the medicine has been considered to result in moderate environmental risk.”
PEC/PNEC > 10	“Use of the medicine has been considered to result in high environmental risk.”

If there is not sufficient data to calculate the PEC/PNEC, the following statement is used:

“Risk of environmental impact cannot be excluded due to lack of data.”

In the case where the PEC:PNEC<1, but the medicine is considered as having potential PBT or vPvB (very Persistent, very Bioaccumulative), the risk phrase is replaced with the phrase:

“Hazardous environmental properties.”

At the **prescriber level**, the environmental risk information given to patients is repeated, but it also includes additional information on the environmental persistence (degradation) and bioaccumulation of the active substance.

Degradation: “The medicine is degraded in the environment”, or  
 “The medicine is slowly degraded in the environment”, or  
 “The medicine is potentially persistent”.

Bioaccumulation: “No significant bioaccumulation potential”, or  
 “Potential to bioaccumulate in aquatic organisms”.

If the pharmaceutical fulfills the criteria for PBT and/or vPvB, the following phrase is added:

“According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.”

If there is insufficient data to characterize the potential for degradation, the following statement is used:

The potential for persistence cannot be excluded due to lack of data.

If there is insufficient data to characterize the potential for bioaccumulation, the following statement will be used:

The potential for bioaccumulation cannot be excluded due to lack of data

At the **specialist level**, all environmental information available is provided. Some examples are (Apoteket, 2006):

- Risk assessment, i.e. PEC/PNEC, calculations as well as the specific PEC and PNEC calculation, given in microgram/l, where applicable.
- Total sold amount in kilograms of the active substance on the market (including all products and enantiomers containing the same active substance) in the most recent year for which data are available.
- Results from ecotoxicity tests (given in microgram/l).
- Test guidelines used (e.g. OECD, FDA).
- Information about which forms the pharmaceutical is excreted as, parent compound as well as metabolites, and the percentages thereof.
- Data interpretation in the context of risk and hazard assessment.

(The shortcomings involved in the available information and the methodology being used are highlighted in Apoteket (2006).)

Summarising, the system delivers in its first stage information on the *environmental risk* associated with the active pharmaceutical ingredient. This information is based on the intrinsic characteristics of the substance, and real or predicted figures for its use *in Sweden*. In

the second phase, the prescriber also has at his/her disposition information regarding the substance's *hazard*, i.e. of similar nature to the information contained in the Stockholm model. The final, specialist level includes all information available for the substance. Every year, the evaluation of new active substances is made public (around 50 substances were added to the list in 2007), and the Council expects all active ingredients in the Swedish market to have been assessed for their environmental risks by 2010 (Stockholm City Council, 2007).

Because European regulations strictly control the information that can appear on pharmaceutical packaging, the information is distributed through other channels. The Swedish pharmaceutical industry, already counting with a popular web-portal ([www.fass.se](http://www.fass.se)), publishes all three levels on its website (predominantly in Swedish but recently more data are published in English). The Stockholm City Council, on the other hand, publishes yearly booklets (both in Sweden and in English) with the updated information; this information is also made available on the internet. In addition to providing this information, Stockholm City Council gives prescribers a series of recommendations, such as to encourage patients to return their unused medications at pharmacies, inform patients of the importance of returning estrogen patches, prescribe starter packs, review and regularly reassess the patient's total consumption of medication in order to reduce waste, etc.

A factor that contributes to the success of the system but, in the same time, makes it difficult to transfer elsewhere is the fairly unique situation of PP sales statistics' availability in Sweden because of the Apoteket monopoly of the PP market. Elsewhere, data of similar extent and completeness, will be available with difficulty.

The possibilities of the Swedish model for limiting the discharge of pharmaceuticals into the environment seem considerable. Particularly when considering doctor's high compliance with expert groups' recommendations, the informing of both doctors and patients on the environmental aspects of their prescription practices, and the general awareness-raising regarding this issue, the approach seems to have considerable potential.

A research project is now ongoing to measure in a quantitative way the actual effect of the Swedish classification system in changing consumer behaviour.

### 3.3.2.3 The industry's position on the classification scheme

A recent article (March 2007) in the Regulatory Affairs Journal provides insight into the industry's position on the classification scheme (all authors are members of the Swedish Association of the Pharmaceutical Industry (LIF)). The industry's motivation for participating in such a scheme, and providing environmental information, can be summed up as follows:

- “The Swedish County Councils [...] increasingly suggested that environmental effects should in future be included in the factors that the regional drug committees took into account when making recommendations to doctors on which medicines to prescribe.”
- “It was also suggested that environmental data should be one of the factors taken into account when County Councils applied for tenders on pharmaceutical products.”
- The risk of not participating in the Swedish debate, i.e. not providing its information on the environmental behaviour of pharmaceuticals and not participating in the design of a classification scheme, would have implied “raising the risk of new constraints in the form of regulations imposed on industry by legislative bodies” (all quotes Mattson et al., 2007).

In parallel with the Swedish task force, which included players from the health sector, and a reference group with stakeholders, the industry set up an international task force with experts “with internationally recognised environmental expertise from several pharmaceutical companies, i.e. Pfizer, AstraZeneca, Merck, GSK, Lilly and Roche.” It is thus clear that the industry took the process very seriously, and that it is conscious of the fact that the classification system “has been the subject of considerable interest in Sweden and abroad”.

Although the industry presents itself as one of the drivers of the process that created the voluntary scheme, at the same time it also puts in question the large efforts invested in this system; for this, it is based on its observation that so far only two active pharmaceutical ingredients have been classified as actually presenting “high” environmental risk. Nevertheless, the industry sees in a positive light the fact that it has become a relevant and to some extent trusted stakeholder in this issue, which could be of importance if the subject of the environmental impact of pharmaceuticals becomes more contentious in the future (Mattson et al., 2007). Also of importance for the industry is that this classification scheme, and not another, would be the basis for environmental criteria which may be incorporated into County Council tenders in the future. This would be of central importance due to the huge clout of the County Councils in the Swedish health system.

### **3.3.3 Activities supportive of policy**

Other activities to be considered as supportive of policy are Swedish research efforts and some outstanding efforts addressing outreach.

The MPA report commissioned by the Swedish government in 2004 (MPA, 2004) was also to “include a risk assessment of environmental effects based on the occurrence of the products in the environment in relation to their current sales volumes”. Of the approximately 1,200 active pharmaceutical ingredients (APIs) on the Swedish market, the study prioritised 30 APIs for hazard assessment and 27 for environmental risk assessment, based on retail sales, biodegradability, and literature (the study also highlighted the deficient or non-existent data for most of the APIs). The lack of data implied that hazard assessments were only possible for 12 of the 30 APIs: 9 of the 12 were assessed to be hazardous to the environment. Environmental risk assessments were carried out for 22 of the 27 APIs: two were found to be associated with negative effects on the aquatic environment. According to the study, “the results indicate that today’s use of pharmaceuticals does not involve any acute environmental risks, but do not exclude the possibility for long-term environmental risks.”

The study was more successful in highlighting the problem of lack of knowledge in this scientific field, and the areas which should be given priority. Lack of knowledge was also the main reason behind the report not supporting the development of an environmental classification system. An article summarising the report’s results stated: “There is a growing interest in introducing an environmental classification system for pharmaceuticals in Sweden. The lack of solid scientific data does, however, lead to practical problems and the risk of arriving at erroneous conclusions is apparent” (Carlsson, 2006). The report concludes that “there is an urgent need to increase our knowledge of the environmental effects of pharmaceutical products and this need for research should be recognised and given priority within the area of environmentally directed research” (MPA, 2004).

Additional efforts have targeted these research needs. A major study is currently underway, addressing the information gaps for the approx. 35 most relevant pharmaceuticals (based on consumption levels and behaviour in the environment; Koschorreck, pers. comm.). Studies have been undertaken which address the actor side of the problem, researching for instance the reasons why medicines are returned to Swedish pharmacies unused (Ekedahl, 2006).

Regarding outreach, there have been very important efforts targeting the communication of the scientific background to the public. The most notable is the book “Environment and Pharmaceuticals”, collaboratively produced between Apoteket, Stockholm University, and the Stockholm City Council, and published by Apoteket (2006). This book is available for download both in English and Swedish on Apoteket’s website, and explains for instance the basics of ecotoxicology, hormones and endocrine-disrupting substances in the environment, the workings of a treatment plant, and the precautionary principle.

Other information, also made available on the internet in both Swedish and English, are provided by the Stockholm City Council, for instance in the form of booklets (e.g. Environmentally Classified Pharmaceuticals, 2007).

Finally, all the environmental risk assessment information for the pharmaceuticals evaluated under the “Swedish model” is available online under [www.fass.se](http://www.fass.se).

As far as monitoring of PPs in the water environment is concerned, in some Swedish counties (e.g. the Stockholm County) regular monitoring of selected substances is carried out in their most important water bodies, depending on the decision of the individual County Councils.

## 4 Discussion of current policy instruments

In this section, the current policy framework and its instruments to limit the discharge of pharmaceutical products (PPs) is discussed, with regard to its relevance for the protection of the aquatic environment. The discussion is based on the authors' own assessment in the present review as well as on existing commentaries of other experts in this field.

In general, environmental policy responses to water pollution are, as a rule, based on certain principles: the precautionary principle, the principle that pollution should be avoided at source, the prevention principle, as well as the polluter-pays principle.

Current EU policies related to risk reduction from the presence of PPs in the environment can be seen in the context of the precautionary and prevention principles, but also in the context of end-of-pipe solutions (mainly wastewater treatment aspects). Having said that, it should be kept in mind that, in current EU environmental policy, precautionary and preventive approaches instead of end-of-pipe solutions are being promoted at all decision and policy levels.

### 4.1 Policy framework in the light of the precautionary and prevention principles

The precautionary principle emphasises that, where evidence of a threat to the health of the environment exists, scientific uncertainty must not be allowed to delay reasonable forms of management action. Therefore, given that concerns exist that pharmaceuticals in natural waters could have subtle, long-term effects on the reproduction, development, and/or behaviour of aquatic species, uncertainty should not be a reason to allow environmental contamination by pharmaceuticals to continue unabated. This urges the scientific and policy community to consider and possibly to implement management strategies to mitigate the release of PPs to the environment (Doerr-MacEwen & Haight, 2006).

On the other hand, there are arguments that the interpretation and possible application of the precautionary principle need to be adapted to the conditions of pharmaceutical risk management. The precautionary principle has evolved in the setting of environmental policy making, a field with significant differences to the characteristics of pharmaceutical risk management (Callréus, 2005). In a recent review of expert stakeholders' views on the management of pharmaceuticals in the environment, concerns were expressed about the precautionary principle. These concerns were related mainly to the proportionality of management action, the balancing of risks and socioeconomic considerations, and the level of scientific evidence required to engage in precautionary management action. Despite concerns, however, a number of risk management strategies for PPs in the environment such as drug take-back schemes were considered by most as sensible approaches (Doerr-MacEwen & Haight, 2006).

All in all, environmental concerns are now more strongly integrated in EU regulations on PPs than in the past, at least with respect to the marketing authorisation of PPs. As already mentioned, since September 2005, each new human medicine must undergo environmental risk assessment, while in the case of veterinary medicine authorisation, environmental security has gained the same weight as consumer security in the risk-benefit analysis. Also, detailed guidelines are now available for the environmental risk assessment procedure of both human and veterinary medicine.

Nevertheless, certain gaps still exist in the medicinal policy framework and in the practical aspects of its implementation; these should be targeted in future efforts addressing the



presence of PPs in the environment. In this context, the authors would like to emphasise the following issues:

- **Environmental safety of “old medicine”.** So far, environmental risk is not assessed for so-called “old medicine”. “Old medicine” includes products authorised before the adoption of EU legislation requesting environmental risk assessment (in 1993 for human PPs and in 1990 for veterinary PPs) and the adoption of relevant ERA guidelines (in 2006 for human PPs and in 1998 for veterinary PPs). “Old medicine” indeed constitutes a large proportion of medicinal products authorised and available on the market, and there is currently no system for their environmental evaluation and control. It is argued that, in analogy to provisions for industrial chemicals, biocides and pesticides, the environmental safety of “older medicine” (both human and veterinary) should also be assessed. Priority lists for an “old medicine” programme should be drafted, and applied at the European level to minimise the environmental evaluation work load (SRU, 2007).
- **Authorisation of veterinary medicine and risk mitigation.** Doubts about the acceptability of the environmental impact of veterinary medicine can lead to changes of the characteristics of the product, of the area of its application, or even to the refusal of marketing authorisation by the authorities. An identified environmental impact may also be mitigated to an acceptable level by special precautions included in the information that accompanies the product in labeling and packaging. Such precautions can include the application of manure coming from treated animals at a minimum distance from surface waters, restrictions to the direct access of treated animals to surface waters. The addressees of such precautionary measures are livestock owners and those responsible for handling manure.

Montforts (2005), however, identified several constraints which decrease the technical and legal effectiveness of such measures. On the one hand, measures taken on the basis of the relevant medicinal Directive (2001/82/EC) are not legally binding for veterinary doctors and farmers (the consumers). Therefore, there seems to be a need for complementary regulations with regard to PP application instructions and their addressees in national legislation in a Europe-wide harmonised manner. On the other hand, precautionary measures are only acceptable under the medicinal Directive 2001/82/EC if their effect can be demonstrated using risk assessment methodologies. For measures completely prohibiting the release of treated animals or the use of contaminated manure, it is quite easy to demonstrate that they have an effect. However, the impact of temporary storage of contaminated manure or of keeping a security distance of treated animals from surface waters cannot be easily quantified due to the lack of standardised methods. Therefore, to render these precautionary measures effective for risk mitigation, and hence suitable for labelling and packaging, the risk assessment methodology should be further developed and applied adequately.

- **Authorisation of human medicine and risk mitigation.** Although approval of authorisation for veterinary medicines can be refused on the basis of risks to the environment, this is not the case for human medicine. The principle therein is that the therapeutic benefit for sick humans is to be considered beyond possible damages to the environment. This principle can doubtless be followed; however, a possible future approach could for instance require that the therapeutic benefit be superior to any alternatives and that a broad, little-controllable application (e.g. via recipe-free circulation for self-medication) be prevented. Thus, although it is unrealistic to prohibit the authorisation of human PPs on environmental grounds, different alternatives should be considered in the authorisation process to reduce environmental exposure as far as possible (SRU, 2007). If alternative compounds are available promising the same success

in therapy, but posing at the same time a lower environmental risk, a refusal of authorisation should not be excluded per se (Knacker et al., 2006).

Furthermore, if certain human PPs are marketed despite their significant risk for the environment, strict take-back schemes should be implemented for their collection and safe disposal. Such binding measures would ensure that the PP marketing authorisation process takes better account of the environment. This points in the direction of clearer linkage of the environmental risk assessment of PPs to management outcomes, a shortcoming also identified by expert stakeholders in the review of Doerr-MacEwen & Haight (2006).

It should also be mentioned that, in general, almost no experience for human medicine in the risk management area has been gathered so far (Koschorrek & Apel, 2006). At the moment, there is no concrete proposal and no binding regulations for mitigation measures relevant to human medicine (SRU, 2007). It is however expected that the 2006 publication of the EMEA guideline on the ERA of human PPs will contribute to the broader use of risk mitigation measures for human PPs.

- **Drug take-back schemes.** The extent of establishment and the degree of effectiveness of take-back schemes for drugs is quite different among European countries. In-depth assessments of scheme effectiveness (estimated recovery rate of unused/expired drugs) are missing to a great extent. High levels of public awareness and education, firstly regarding the environmental consequences of the disposal of unused/expired drugs and, secondly, on the operation of such schemes seem to be key for their success. Problems in the implementation of take-back schemes are largely related to lack of awareness, leading to erroneous consumer behaviour. There is thus need to improve the labelling of pharmaceuticals and consumer information, so as to assure the return of unused pharmaceuticals to pharmacies.

As far as the EU policy framework beyond medicinal regulations is concerned, at present it does not adequately take account of the precautionary and prevention principles on the issue of pharmaceuticals in the environment; this is partly due to implementation deficiencies and partly due to legislation gaps. However, it is not argued here that additional directives are needed. A suitable EU policy framework seems already to be in place, but possibly the modification of existing directives may be needed:

- **Water Framework Directive.** The WFD provides an appropriate policy framework to deal with all sources of chemical pollution in European waters if implemented properly.

Firstly, it establishes a list of priority chemical substances for which measures must be progressively applied to reduce their concentration below defined quality standards. It is argued that in future revisions of the list of priority substances, certain PPs should be included; for such PPs, environmental quality objectives should then be defined.

Secondly, the WFD (Annex VIII) requires to identify all other pollutants that are discharged in significant quantities in the river basins and to set relevant quality standards that should be met by 2015 as part of good ecological status. The definition of target substances and standards is up to the Member States and to specific basin authorities. For instance, in the UK, two PPs are under discussion for addition to the list of UK specific pollutants according to WFD Annex VIII.

However, all in all, the respective WFD mechanisms and the Directive's precautionary principle are not yet used fully to deal in a focused way with the issue of PPs in the



aquatic environment. The issue is currently not politically discussed, which is partly due to its complexity, uncertainties, and lack of knowledge (as described in the next section).

A first important step in order to better use the WFD implementation process for filling in knowledge gaps on PPs in the aquatic environment is to include PPs in the so-called “characterisation of river basin districts and review of environmental impact of human activity” (WFD Art. 5), which includes a pressures and impacts assessment of all water bodies.

On the basis of the Art. 5 “river basin district characterisation” results, decisions for future monitoring of substances and relevant necessary water management measures can be taken. Appropriate and adequate monitoring of pharmaceutical substances in the environment is in general missing. It is recommended to include the monitoring of specific pharmaceutical substances - those which are of high environmental relevance due to the effects, persistence or mobility - in existing monitoring programmes like those for the WFD implementation (SRU, 2007).

- **Drinking Water & Groundwater Directives.** PPs are not listed yet in the Annexes of these two key water directives that refer to substances to be monitored. Nevertheless, with respect to drinking water (whose source is often groundwater), there is frequently concern on possible health impacts due to the presence of PPs. Firstly, public demand for drinking water of good quality - free of any chemical substances - cannot be overlooked by water managers. Secondly, the precautionary principle is often called for in this case, when bearing in mind uncertainties such as the following: the increasing spread of antibiotic-resistant bacteria can pose a health risk for humans; there is lack of knowledge on risk to human health (via drinking water) from chronic exposure to PPs that are designed for short-term use.
- **Bathing Water Directive.** The recent amendment of the Bathing Water Directive may be seen as a step forward when discussing this Directive in the overall framework of new EU water policies. However, due to several implementation gaps of the overall framework and especially the fact that PPs are currently not widely discussed in WFD implementation, there is the risk that the issue of PPs in bathing waters will not receive adequate attention in policy implementation.
- **Other environmental policies and initiatives.** The following refers to European soil policy, the Sewage Sludge Directive, the EU Endocrine Strategy, the REACH Regulation, and the IPPC Directive:
  - PPs are not yet part of current policy documents under discussion on *European soil protection*. However, the possible relevance of European soil protection for PPs has been identified on a policy level by placing these substances among the priority issues for further research in this field (in terms of their quantification and risk evaluation methods).
  - Despite the fact that PPs’ presence in sewage sludge could lead to the unintended uptake of relatively high concentrations of PPs via food consumption (when food is grown on fields where sewage sludge is applied), there are no limits for PP concentrations yet in the *Sewage Sludge Directive*. Another possible fate for pharmaceuticals and other pollutants contained in sewage sludge is their being leached into groundwater, and eventually making their way into surface water and/or drinking water. In fact, in some EU countries, due to preoccupation with the issue of contaminants in sludge, including pharmaceuticals, the application of sewage sludge on agricultural fields has been prohibited.

- An identification and evaluation process of substances with potential environmental and health impacts of endocrine disruption continues and improves in the context of the *Endocrine Strategy*. Any pharmaceuticals detected under the Endocrine Strategy efforts will be dealt with in existing environmental regulation as far as possible. For the aquatic environment, the endocrine strategy also refers to the WFD and its strategy against pollution.
- PPs are also exempt from the main provisions on registration, evaluation, authorization, and downstream use of chemicals in the EU *REACH Regulation*. Some provisions of REACH remain applicable, including disclosure of information (on hazardous properties and regarding risk management measures) and restrictions on marketing and use of substances that pose an “unacceptable” health or environmental risk. However, these provisions will probably rarely be applied to medicinal products.
- The *IPPC Directive*, which aims at pollution prevention and control in industrial production processes, only applies to the production of PPs. This Directive ensures that emission of PPs into the environment during production is minimised. There has been much progress in reducing emissions of PPs in the production phase by respecting relevant legislation and by improving the technologies used in industrial manufacturing. In consequence, efforts to further limit the discharge of PPs into the environment should concentrate on steps beyond (but also prior to) production.
- Finally, when considering the EU policy framework in its entirety, it becomes obvious that a **closer linkage between medicinal policies and environmental protection policies**, when it comes to PP environmental risk assessment, would be sensible. ERA decision criteria for the authorisation of medicine and EU environmental directives should be more harmonised with one another, since EU environmental legislation (e.g. the WFD) must provide a common basis for all environmental goals in Europe. At present, the EMEA guidelines for the ERA of pharmaceutical products do not make any explicit reference to relevant EU directives for the protection of water and soil resources. As far as the water environment is concerned, the ERA of PPs should be related to actual water quality standards for both surface and groundwater.

## 4.2 Policy framework and end-of-pipe solutions

Once PPs are released by consumers into sewage, either via urine or after disposal of unused/expired drugs down the drain, only an end-of-pipe solution remains to limit the presence of PPs in the natural aquatic environment.

Although precautionary and pollution preventive policy approaches should be a priority, the policy framework can also be improved in terms of PP removal in the phase of wastewater treatment. The most relevant EU policy is the Urban Wastewater Treatment Directive (UWWTD) which focuses on the reduction of organic material and nutrients. The removal of other pollutants, including pharmaceuticals and heavy metals, has so far only been a side-effect of wastewater treatment.

Besides the full implementation of the Directive in all EU Member States, a future amendment of the UWWTD could be envisioned to include emissions limits on further parameters, e.g. pharmaceuticals. Requirements to deal with pharmaceutical loads in wastewater may also result for plant operators from the WFD. Given the new combined approach of the WFD on water quality, that combines emissions limit values with environmental water quality standards, operators of urban wastewater treatment plants may be forced to upgrade their technologies. In any event, new technologies like ozonation and

membrane filtration, which could improve the degree of removal of PPs from wastewater, have been developed.

The wastewater treatment policy framework can also be modified to intensify efforts for installing special (pre-)treatment facilities for hospital wastewater. Hospital effluents are considered hotspots for water contamination with pharmaceuticals. In consequence, treating their wastewater at source would lessen the treatment load in the larger urban treatment facilities.

However, in this discussion a crucial issue is the cost recovery for investments in new treatment technologies. Next to regulatory modifications, economic instruments (e.g. earmarked water taxes) could be used to financially support further treatment. In this context, it is also important to clarify the role of the polluter (industry or consumer) in order to develop an appropriate approach for implementing the polluter-pays principle.

### 4.3 What complicates further EU policy development to limit discharge of PPs into waters?

Based on the discussion provided in the two previous sections, it is apparent that there are still certain gaps (either legislative gaps or implementation gaps of existing legislation) in the current policy framework that deals with the discharge of PPs into the aquatic environment. Taking further action to close some of these gaps is, however, still difficult, due to lack of relevant information and knowledge as well as uncertainties on PPs in the environment.

It becomes clear that we need **better understanding, better data and further research** on PPs in the aquatic environment. Some of the key issues to be clarified include:

- **Knowledge on the fate and effects of PPs in the environment.** So far, knowledge on the fate and effects of PPs in the environment has been sparse. It is hoped, however, that given the recent adoption of EU guidelines on the ERA of PPs, more data on the fate and effects of PPs will be generated in the near future (Koschorreck & Apel, 2006).
- **Knowledge on low-level effects and chronic effects of PPs.** The environmental risk assessment for PPs should guarantee that possible low level and long-term effects of PPs are not overlooked. The strict application of an action limit, which terminates any further risk assessment for substances not exceeding the PEC in surface water (0.01µg/L for human medicine), may lead to the disregard of such effects, considering that experience with the ecotoxicological effects of human PPs is still very limited.

Concerning chronic effects, data need to be made available that allow their assessment in ecotoxicological studies, especially for products that have been on the market for a long time.

Concerning low-level effects, there is a strong opinion that pharmaceutical compounds do not pose a large risk because they are present in such low concentrations (ng/l), with most effects only seen in the mg/l range. However, it should be kept in mind that disease resistance to pharmaceuticals is favoured by low concentration exposure and compounds such as hormones have effects at very low levels. The effects of active compounds in the low (ng/l range) cannot be excluded, as experience with pesticides has shown, impacts can be significant at low levels (Stuer-Lauridsen et al., 2000).

- **Cumulative effects of multiple PP substances.** Although in the environment organisms are exposed to a variety of substances, the potential impact of mixtures of individual substances in the environment is recognised as an unresolved issue within the currently implemented ERA schemes. Especially in the case of pharmaceuticals from similar

medicinal classes, it can be expected that they have similar modes of action under environmental conditions, and hence, additive or synergistic effects are likely to occur (Knacker et al., 2006). So far, only individual products undergo an environmental risk assessment and thus, the risk assessment process is lacking in cumulative assessments of potential environmental risk from substances of comparable structure (SRU, 2007).

- **General data availability and accessibility.** At present, the low quality of data used in ERA and the difficulty to access ERA information used in marketing authorisation remain key problems for several interested stakeholders. Reliable consumption figures for all authorised substances are missing. There is also great unbalance between newly authorised PPs and PPs already on the market in terms of the data that can be used for evaluations (SRU, 2007). The ERA data and information are only open to the respective national competent authorities (with the exception of Sweden where ERA results are made public online on a voluntary basis). The UK Environment Agency argues for open access to non-commercially sensitive information to facilitate effective environmental assessments. It has thus called upon the EMEA and the MHRA (the English equivalent) to put in place a suitable system making environmental information on pharmaceuticals easily available and accessible (Environment Agency, 2003).

Another important data limitation concerns figures for medication consumption. In most countries, and for both human and veterinary products, no reliable figures for pharmaceutical use are available. This is an important stumbling block when trying to determine the environmental impacts of the use of human and veterinary pharmaceuticals. A possible way of addressing this issue is to increase the requirements regarding the documentation of use (SRU, 2007).

There are several national but also European projects currently addressing relevant knowledge and information gaps. The EU KNAPPE project, which aims at consolidating and advancing knowledge on PPs in environmental waters, will develop a classification system to prioritise environmental risks of PPs. It will also identify PPs of most concerns which should be integrated in future monitoring programmes. Furthermore, the EU ERAPharm project (<http://www.erapharm.org>) is explicitly dedicated to advancing existing knowledge and methods for evaluating potential risks of human and veterinary PPs to the environment. Readers interested in the latest scientific recommendations for improvements in ERA should refer to the results of the ERAPharm project that will be published shortly.

Besides the scientific and data gaps highlighted above, the following issue also complicates further policy discussions on PPs in the environment:

- The difficulty of setting regulatory limits on the release of PPs into water from different sources (the public, wastewater treatment plants, industry) and of applying economic instruments (e.g. taxes to finance pollution-reduction measures), is the question of “**who is the polluter**”. Different definitions of the polluter (consumers of medicine; industry; doctors as prescribers; hospitals; pharmacists; or even public agencies issuing PP marketing authorisations) can be used, with varying implications. It is thus important to clarify who the polluter is and to carry out research on the costs and benefits of the different options.

Clarifying this issue is also key for applying the “**polluter-pays principle**” of the Water Framework Directive. The “polluter-pays principle” is however even more difficult to clarify and apply in the case of diffuse water pollution from the use of veterinary medicine.

All in all, the development of further policy options and instruments to limit the discharge of PPs into the aquatic environment requires an open consultation and dialogue process between key public and private stakeholders. The need to develop further policy or amend existing policy has to be based on a balanced consideration of the following: the precautionary and prevention principles used in environmental policy making, the polluter-pays principle, but also new scientific knowledge arising on the risks and impacts of the unintended release of PPs into water (see results of research projects such as KNAPPE and ERAPharm).

Finally, it should be noted that further approaches to limit the discharge of PPs into the aquatic environment are also under discussion, which go beyond product authorisation regulations and the policy framework of existing Directives. In this context, the following actors can play a role in various ways: the industry (e.g. by better communication of the risk of certain substances via “green labelling”, by developing new specific product forms or by introducing environmental criteria in the early steps of product development), the public domain (e.g. by promoting and ensuring safe waste disposal with incineration), the health care system, doctors as well as patients (e.g. by responding to communication efforts on the environmental risk of PPs, making better use of drug take-back schemes etc.).



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